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| Url: https://pubmed.ncbi.nlm.nih.gov/36803626 DOI: https://doi.org/10.1186/s13293-023-00496-w  Title(2023): Investigation of autism-related transcription factors underlying sex differences in the effects of bisphenol A on transcriptome profiles and synaptogenesis in the offspring hippocampus.  Bisphenol A (BPA) has been linked to susceptibility to autism spectrum disorder (ASD). Our recent studies have shown that prenatal BPA exposure disrupted ASD-related gene expression in the hippocampus, neurological functions, and behaviors associated with ASD in a sex-specific pattern. However, the molecular mechanisms underlying the effects of BPA are still unclear. Transcriptome data mining and molecular docking analyses were performed to identify ASD-related transcription factors (TFs) and their target genes underlying the sex-specific effects of prenatal BPA exposure. Gene ontology analysis was conducted to predict biological functions associated with these genes. The expression levels of ASD-related TFs and targets in the hippocampus of rat pups prenatally exposed to BPA were measured using qRT-PCR analysis. The role of the androgen receptor (AR) in BPA-mediated regulation of ASD candidate genes was investigated using a human neuronal cell line stably transfected with AR-expression or control plasmid. Synaptogenesis, which is a function associated with genes transcriptionally regulated by ASD-related TFs, was assessed using primary hippocampal neurons isolated from male and female rat pups prenatally exposed to BPA. We found that there was a sex difference in ASD-related TFs underlying the effects of prenatal BPA exposure on the transcriptome profiles of the offspring hippocampus. In addition to the known BPA targets AR and ESR1, BPA could directly interact with novel targets (i.e., KDM5B, SMAD4, and TCF7L2). The targets of these TFs were also associated with ASD. Prenatal BPA exposure disrupted the expression of ASD-related TFs and targets in the offspring hippocampus in a sex-dependent manner. Moreover, AR was involved in the BPA-mediated dysregulation of AUTS2, KMT2C, and SMARCC2. Prenatal BPA exposure altered synaptogenesis by increasing synaptic protein levels in males but not in females, but the number of excitatory synapses was increased in female primary neurons only. Our findings suggest that AR and other ASD-related TFs are involved in sex differences in the effects of prenatal BPA exposure on transcriptome profiles and synaptogenesis in the offspring hippocampus. These TFs may play an essential role in an increased ASD susceptibility associated with endocrine-disrupting chemicals, particularly BPA, and the male bias of ASD. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/35112480 DOI: https://doi.org/10.1002/aur.2680  Title(2022): Association between atopic diseases and neurodevelopmental disabilities in a longitudinal birth cohort.  Reports on the association between the prevalence of atopic diseases and neurodevelopmental disabilities (NDs) have been inconsistent in the literature. We investigated whether autism spectrum disorder (ASD), attention deficit-hyperactivity disorders (ADHD), and other NDs are more prevalent in children with asthma, atopic dermatitis (AD) and allergic rhinitis (AR) compared to those without specific atopic conditions. A total of 2580 children enrolled at birth were followed prospectively, of which 119 have ASD, 423 have ADHD, 765 have other NDs, and 1273 have no NDs. Atopic diseases and NDs were defined based on physician diagnoses in electronic medical records. Logistic regressions adjusting for maternal and child characteristics estimated the associations between NDs (i.e., ASD, ADHD, and other NDs) and asthma, AD and AR, respectively. Children with asthma, AD or AR had a greater likelihood of having ADHD or other NDs compared with children without specific atopic conditions. The association between ASD and asthma diminished after adjusting for maternal and child factors. Either mothers or children having atopic conditions and both mothers and children with atopic conditions were associated with a higher prevalence of ADHD in children, compared with neither mothers nor children having atopic conditions. Children diagnosed with multiple atopic diseases were more likely to have NDs compared with those without or with only one type of atopic disease. In conclusion, in this U.S. urban birth cohort, children with atopic diseases had a higher co-morbidity of NDs. The findings have implications for etiologic research that searches for common early life antecedents of NDs and atopic conditions. Findings from this study also should raise awareness among health care providers and parents about the possible co-occurrence of both NDs and atopic conditions, which calls for coordinated efforts to screen, prevent and manage NDs and atopic conditions. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/35042285 DOI: https://doi.org/10.30773/pi.2021.0094  Title(2022): The Relationship of Steroid Hormones, Genes Related to Testosterone Metabolism and Behavior in Boys With Autism in Slovakia.  Purpose of the study was to identify the relationship among actual plasmatic levels of steroid hormones and behavioral manifestations in boys with autism and to assess the genetic contribution to these manifestations. 172 boys with autism under 10 years of age and 135 neurotypical boys attended the study. ADI-R and ADOS-2 were used to evaluate the core symptom severities. Problem behavior was assessed using BPI-01 questionnaire. Levels of testosterone, estradiol, dehydroepiandrosterone, dehydroepiandrosterone-sulfate and sex hormone binding globulin (SHBG) were measured in plasma of autistic boys. Three SNPs (in ESR1, SHBG, SRD5A2 genes) and one STR in AR gene (number of CAG repeats in first exon) were assessed. Hormonal levels and number of CAG repeats in AR gene were used for correlation analysis with behavioral measures. Genotype and allelic frequencies were compared among autistic and neurotypical boys. We found negative relationship among SHBG levels and restricted, repetitive behaviors (measured by ADOS-2) and positive relationship among actual testosterone levels and frequency of stereotyped behavior (measured by BPI-01). Actual levels of SHBG and testosterone are related to severities of restricted and repetitive behaviors in boys with autism. Mechanisms of action of these hormones in brain require further investigation. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/34947998 DOI: https://doi.org/10.3390/ijms222413201  Title(2021): Autism-Related Transcription Factors Underlying the Sex-Specific Effects of Prenatal Bisphenol A Exposure on Transcriptome-Interactome Profiles in the Offspring Prefrontal Cortex.  Bisphenol A (BPA) is an environmental risk factor for autism spectrum disorder (ASD). BPA exposure dysregulates ASD-related genes in the hippocampus and neurological functions of offspring. However, whether prenatal BPA exposure has an impact on genes in the prefrontal cortex, another brain region highly implicated in ASD, and through what mechanisms have not been investigated. Here, we demonstrated that prenatal BPA exposure disrupts the transcriptome-interactome profiles of the prefrontal cortex of neonatal rats. Interestingly, the list of BPA-responsive genes was significantly enriched with known ASD candidate genes, as well as genes that were dysregulated in the postmortem brain tissues of ASD cases from multiple independent studies. Moreover, several differentially expressed genes in the offspring's prefrontal cortex were the targets of ASD-related transcription factors, including AR, ESR1, and RORA. The hypergeometric distribution analysis revealed that BPA may regulate the expression of such genes through these transcription factors in a sex-dependent manner. The molecular docking analysis of BPA and ASD-related transcription factors revealed novel potential targets of BPA, including RORA, SOX5, TCF4, and YY1. Our findings indicated that prenatal BPA exposure disrupts ASD-related genes in the offspring's prefrontal cortex and may increase the risk of ASD through sex-dependent molecular mechanisms, which should be investigated further. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/33248253 DOI: https://doi.org/10.1016/j.neuroimage.2020.117594  Title(2021): Characterization of mice bearing humanized androgen receptor genes (h/mAr) varying in polymorphism length.  The androgen receptor (AR) is known for masculinization of behavior and brain. To better understand the role that AR plays, mice bearing humanized Ar genes with varying lengths of a polymorphic N-terminal glutamine (Q) tract were created (Albertelli et al., 2006). The length of the Q tract is inversely proporitional to AR activity. Biological studies of the Q tract length may also provide a window into potential AR contributions to sex-biases in disease risk. Here we take a multi-pronged approach to characterizing AR signaling effects on brain and behavior in mice using the humanized Ar Q tract model. We first map effects of Q tract length on regional brain anatomy, and consider if these are modified by gonadal sex. We then test the notion that spatial patterns of anatomical variation related to Q tract length could be organized by intrinsic spatiotemporal patterning of AR gene expression in the mouse brain. Finally, we test influences of Q tract length on four behavioral tests.Altering Q tract length led to neuroanatomical differences in a non-linear dosage-dependent fashion. Gene expression analyses indicated that adult neu- roanatomical changes due to Q tract length are only associated with neurode- velopment (as opposed to adulthood). No significant effect of Q tract length was found on the behavior of the three mouse models. These results indicate that AR activity differentially mediates neuroanatomy and behavior, that AR activity alone does not mediate sex differences, and that neurodevelopmen- tal processes are associated with spatial patterns of volume changes due to Q tract length in adulthood. They also indicate that androgen sensitivity in adulthood is not likely to lead to autism-related behaviors or neuroanatomy, although neurodevelopmental processes may play a role earlier. Further study into sex differences, development, other behaviors, and other sex-specific mech- anisms are needed to better understand AR sensitivity, neurodevelopmental disorders, and the sex difference in their prevalence. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/32327976 DOI: https://doi.org/10.3389/fncel.2020.00087  Title(2020): Berberine Ameliorates Prenatal Dihydrotestosterone Exposure-Induced Autism-Like Behavior by Suppression of Androgen Receptor.  Many epidemiology studies have shown that maternal polycystic ovary syndrome (PCOS) results in a greater risk of autism spectrum disorders (ASD) development, although the detailed mechanism remains unclear. In this study, we aimed to investigate the potential mechanism and provide a possible treatment for PCOS-mediated ASD through three experiments: Experiment 1: real-time PCR and western blots were employed to measure gene expression in human neurons, and the luciferase reporter assay and chromatin immunoprecipitation (ChIP) was used to map the responsive elements on related gene promoters. Experiment 2: pregnant dams were prenatally exposed to dihydrotestosterone (DHT), androgen receptor (AR) knockdown (shAR) in the amygdala, or berberine (BBR), and the subsequent male offspring were used for autism-like behavior (ALB) assay followed by biomedical analysis, including gene expression, oxidative stress, and mitochondrial function. Experiment 3: the male offspring from prenatal DHT exposed dams were postnatally treated by either shAR or BBR, and the offspring were used for ALB assay followed by biomedical analysis. Our findings showed that DHT treatment suppresses the expression of estrogen receptor β (ERβ) and superoxide dismutase 2 (SOD2) through AR-mediated hypermethylation on the ERβ promoter, and BBR treatment suppresses AR expression through hypermethylation on the AR promoter. Prenatal DHT treatment induces ERβ suppression, oxidative stress and mitochondria dysfunction in the amygdala with subsequent ALB behavior in male offspring, and AR knockdown partly diminishes this effect. Furthermore, both prenatal and postnatal treatment of BBR partly restores prenatal DHT exposure-mediated ALB. In conclusion, DHT suppresses ERβ expression through the AR signaling pathway by hypermethylation on the ERβ promoter, and BBR restores this effect through AR suppression. Prenatal DHT exposure induces ALB in offspring through AR-mediated ERβ suppression, and both prenatal and postnatal treatment of BBR ameliorates this effect. We conclude that BBR ameliorates prenatal DHT exposure-induced ALB through AR suppression, this study may help elucidate the potential mechanism and identify a potential treatment through using BBR for PCOS-mediated ASD. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/30104728 DOI: https://doi.org/10.1038/s41380-018-0198-y  Title(2020): Sex-specific impact of prenatal androgens on social brain default mode subsystems.  Early-onset neurodevelopmental conditions (e.g., autism) affect males more frequently than females. Androgens may play a role in this male-bias by sex-differentially impacting early prenatal brain development, particularly neural circuits that later develop specialized roles in social cognition. Here, we find that increasing prenatal testosterone in humans is associated with later reduction of functional connectivity between social brain default mode (DMN) subsystems in adolescent males, but has no effect in females. Since testosterone can work directly via the androgen receptor (AR) or indirectly via the estrogen receptor through aromatase conversion to estradiol, we further examined how a potent non-aromatizable androgen, dihydrotestosterone (DHT), acts via the AR to influence gene expression in human neural stem cells (hNSC)-particularly for genes of high-relevance for DMN circuitry. DHT dysregulates a number of genes enriched for syndromic causes of autism and intellectual disability and for genes that in later development are expressed in anatomical patterns that highly correspond to the cortical midline DMN subsystem. DMN-related and DHT-affected genes (e.g., MEF2C) are involved in a number of synaptic processes, many of which impact excitation-inhibition balance. Androgens have male-specific prenatal influence over social brain circuitry in humans and may be relevant towards explaining some component of male-bias in early-onset neurodevelopmental conditions. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/29141583 DOI: https://doi.org/10.1186/s12881-017-0486-4  Title(2017): Clinical and molecular genetic characterization of familial MECP2 duplication syndrome in a Chinese family.  Chromosomal duplication at the Xq28 region including the MECP2 gene, share consistent clinical phenotypes and a distinct facial phenotype known as MECP2 duplication syndrome. The typical clinical features include infantile hypotonia , mild dysmorphic features, a broad range of neurodevelopmental disorders, recurrent infections, and progressive spasticity. This Chinese MECP2 duplication syndrome family includes six patients (five males and one female), and four asymptomatic female carriers. Two kinds of chips including 4x180K CNV + SNP chip and custom 8x60K CNV chip were used to detect MECP2 duplication, and then fluorescent in situ hybridization (FISH) analysis was performed to identify the exact copy number of MECP2. X-chromosome inactivation (XCI) analysis on AR gene was detected for all female family members, and the m icrosatellite analysis on MECP2 was used to validate the recombination event on MECP2 region. The affected male subjects presented with a broad range of neurodevelopmental symptoms (severe intellectual disability, developmental delay, seizure, language deficit, and autism spectrum disorder) as well as facial dysmorphism and other symptoms which were consistent with that of Western patients previous reported. Seizure is reported in Chinese patients for the first time. In addition, we validated three recombination events for the MECP2-duplication allele during maternal transmission due to X homologous recombination. We provided the largest known Chinese pedigree with MECP2 duplication syndrome. The detailed clinical description and molecular genetic characterization in all affected family members further delineate the typical phenotype of this genomic disorder in Chinese population. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/27423376 DOI: https://doi.org/10.1016/j.ijdevneu.2016.07.001  Title(2016): Prenatal exposure to sodium valproate alters androgen receptor expression in the developing cerebellum in a region and age specific manner in male and female rats.  Valproic acid (VPA) is an anti-epileptic drug with teratogenicity activity that has been related to autism. In rodents, exposure to VPA in utero leads to brain abnormalities similar than those reported in the autistic brain. Particularly, VPA reduces the number of Purkinje neurons in the rat cerebellum parallel to cerebellar abnormalities found in autism. Thus, we injected pregnant females on embryonic day 12 either with VPA (600mg/kg, i.p.) or 0.9% saline solution and obtained the cerebellum from their offspring at different postnatal time points. Testosterone has been linked to autism and plays an important role during brain development. Therefore, we identified and analyzed the androgen receptor (AR) by immunohistochemistry and densitometry, respectively. We found VPA decreases AR density in the superficial Purkinje layer only in cerebellar lobule 8 at PN7, but increased it at PN14 compared to control in males. In females, VPA decreased AR density in the superficial Purkinje layer in cerebellar lobule 6 at PN14, but increased it in lobule 9 at the same time point. No differences were found in the deep Purkinje layer of any cerebellar lobule in terms of AR density neither in males nor females. We additionally found a particular AR density decreasing in both superficial and deep regions across development in the majority of cerebellar lobules in males, but in all cerebellar lobules in females. Thus, our results indicate that VPA disrupts the AR ontogeny in the developing cerebellum in an age and region specific manner in male and female rats. Future epigenetic studies including the evaluation of histone deacetylases (HDAC's) might shed light these results as HDAC's are expressed by Purkinje neurons, interact with the AR and are VPA targets. This work contributes to the understanding of the cerebellar development and it might help to understand the role of the cerebellum in neurodevelopmental disorders such as autism. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/27014003 DOI: https://doi.org/10.3389/fnbeh.2016.00041  Title(2016): Neural Androgen Receptors Modulate Gene Expression and Social Recognition But Not Social Investigation.  The role of sex and androgen receptors (ARs) for social preference and social memory is rather unknown. In this study of mice we compared males, females and males lacking ARs specifically in the nervous system, AR(NesDel), with respect to social preference, assessed with the three-chambered apparatus test, and social recognition, assessed with the social discrimination procedure. In the social discrimination test we also evaluated the tentative importance of the sex of the stimulus animal. Novel object recognition and olfaction were investigated to complement the results from the social tests. Gene expression analysis was performed to reveal molecules involved in the effects of sex and androgens on social behaviors. All three test groups showed social preference in the three-chambered apparatus test. In both social tests an AR-independent sexual dimorphism was seen in the persistence of social investigation of female conspecifics, whereas the social interest toward male stimuli mice was similar in all groups. Male and female controls recognized conspecifics independent of their sex, whereas AR(NesDel) males recognized female but not male stimuli mice. Moreover, the non-social behaviors were not affected by AR deficiency. The gene expression analyses of hypothalamus and amygdala indicated that Oxtr, Cd38, Esr1, Cyp19a1, Ucn3, Crh, and Gtf2i were differentially expressed between the three groups. In conclusion, our results suggest that ARs are required for recognition of male but not female conspecifics, while being dispensable for social investigation toward both sexes. In addition, the AR seems to regulate genes related to oxytocin, estrogen and William's syndrome. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/24624060 DOI: https://doi.org/10.3389/fncel.2014.00069  Title(2014): Epigenetic effect of testosterone in the behavior of C. elegans. A clue to explain androgen-dependent autistic traits?  Current research indicates that the causes of autism spectrum disorders (ASDs) are multifactorial and include both genetic and environmental factors. To date, several works have associated ASDs with mutations in genes that encode proteins involved in neuronal synapses; however other factors and the way they can interact with the development of the nervous system remain largely unknown. Some studies have established a direct relationship between risk for ASDs and the exposure of the fetus to high testosterone levels during the prenatal stage. In this work, in order to explain possible mechanisms by which this androgenic hormone may interact with the nervous system, C. elegans was used as an experimental model. We observed that testosterone was able to alter the behavioral pattern of the worm, including the gentle touch response and the pharyngeal pumping rate. This impairment of the behavior was abolished using specific RNAi against genes orthologous to the human androgen receptor gene. The effect of testosterone was eliminated in the nhr-69 (ok1926) deficient mutant, a putative ortholog of human AR gene, suggesting that this gene encodes a receptor able to interact with the hormone. On the other hand the testosterone effect remained in the gentle touch response during four generations in the absence of the hormone, indicating that some epigenetic mechanisms could be involved. Sodium butyrate, a histone deacetylase inhibitor, was able to abolish the effect of testosterone. In addition, the lasting effect of testosterone was eliminated after the dauer stage. These results suggest that testosterone may impair the nervous system function generating transgenerational epigenetic marks in the genome. This work may provide new paradigms for understanding biological mechanisms involved in ASDs traits. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/24151554 DOI: https://doi.org/10.1155/2013/826156  Title(2013): Epigenetics and autism.  This review identifies mechanisms for altering DNA-histone interactions of cell chromatin to upregulate or downregulate gene expression that could serve as epigenetic targets for therapeutic interventions in autism. DNA methyltransferases (DNMTs) can phosphorylate histone H3 at T6. Aided by protein kinase C β 1, the DNMT lysine-specific demethylase-1 prevents demethylation of H3 at K4. During androgen-receptor-(AR-) dependent gene activation, this sequence may produce AR-dependent gene overactivation which may partly explain the male predominance of autism. AR-dependent gene overactivation in conjunction with a DNMT mechanism for methylating oxytocin receptors could produce high arousal inputs to the amygdala resulting in aberrant socialization, a prime characteristic of autism. Dysregulation of histone methyltransferases and histone deacetylases (HDACs) associated with low activity of methyl CpG binding protein-2 at cytosine-guanine sites in genes may reduce the capacity for condensing chromatin and silencing genes in frontal cortex, a site characterized by decreased cortical interconnectivity in autistic subjects. HDAC1 inhibition can overactivate mRNA transcription, a putative mechanism for the increased number of cerebral cortical columns and local frontal cortex hyperactivity in autistic individuals. These epigenetic mechanisms underlying male predominance, aberrant social interaction, and low functioning frontal cortex may be novel targets for autism prevention and treatment strategies. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/24119295 DOI: https://doi.org/10.1186/2040-2392-4-39  Title(2013): Differential recruitment of coregulators to the RORA promoter adds another layer of complexity to gene (dys) regulation by sex hormones in autism.  Our independent cohort studies have consistently shown the reduction of the nuclear receptor RORA (retinoic acid-related orphan receptor-alpha) in lymphoblasts as well as in brain tissues from individuals with autism spectrum disorder (ASD). Moreover, we have found that RORA regulates the gene for aromatase, which converts androgen to estrogen, and that male and female hormones regulate RORA in opposite directions, with androgen suppressing RORA, suggesting that the sexually dimorphic regulation of RORA may contribute to the male bias in ASD. However, the molecular mechanisms through which androgen and estrogen differentially regulate RORA are still unknown. Here we use functional knockdown of hormone receptors and coregulators with small interfering RNA (siRNA) to investigate their involvement in sex hormone regulation of RORA in human neuronal cells. Luciferase assays using a vector containing various RORA promoter constructs were first performed to identify the promoter regions required for inverse regulation of RORA by male and female hormones. Sequential chromatin immunoprecipitation methods followed by quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) analyses of RORA expression in hormone-treated SH-SY5Y cells were then utilized to identify coregulators that associate with hormone receptors on the RORA promoter. siRNA-mediated knockdown of interacting coregulators was performed followed by qRT-PCR analyses to confirm the functional requirement of each coregulator in hormone-regulated RORA expression. Our studies demonstrate the direct involvement of androgen receptor (AR) and estrogen receptor (ER) in the regulation of RORA by male and female hormones, respectively, and that the promoter region between -10055 bp and -2344 bp from the transcription start site of RORA is required for the inverse hormonal regulation. We further show that AR interacts with SUMO1, a reported suppressor of AR transcriptional activity, whereas ERα interacts with the coactivator NCOA5 on the RORA promoter. siRNA-mediated knockdown of SUMO1 and NCOA5 attenuate the sex hormone effects on RORA expression. AR and SUMO1 are involved in the suppression RORA expression by androgen, while ERα and NCOA5 collaborate in the up-regulation of RORA by estrogen. While this study offers a better understanding of molecular mechanisms involved in sex hormone regulation of RORA, it also reveals another layer of complexity with regard to gene regulation in ASD. Inasmuch as coregulators are capable of interacting with a multitude of transcription factors, aberrant expression of coregulator proteins, as we have seen previously in lymphoblasts from individuals with ASD, may contribute to the polygenic nature of gene dysregulation in ASD. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/23801657 DOI: https://doi.org/10.1002/aur.1296  Title(2013): Stem cells as a good tool to investigate dysregulated biological systems in autism spectrum disorders.  Identification of the causes of autism spectrum disorders (ASDs) is hampered by their genetic heterogeneity; however, the different genetic alterations leading to ASD seem to be implicated in the disturbance of common molecular pathways or biological processes. In this scenario, the search for differentially expressed genes (DEGs) between ASD patients and controls is a good alternative to identify the molecular etiology of such disorders. Here, we employed genome-wide expression analysis to compare the transcriptome of stem cells of human exfoliated deciduous teeth (SHEDs) of idiopathic autistic patients (n = 7) and control samples (n = 6). Nearly half of the 683 identified DEGs are expressed in the brain (P = 0.003), and a significant number of them are involved in mechanisms previously associated with ASD such as protein synthesis, cytoskeleton regulation, cellular adhesion and alternative splicing, which validate the use of SHEDs to disentangle the causes of autism. Autistic patients also presented overexpression of genes regulated by androgen receptor (AR), and AR itself, which in turn interacts with CHD8 (chromodomain helicase DNA binding protein 8), a gene recently shown to be associated with the cause of autism and found to be upregulated in some patients tested here. These data provide a rationale for the mechanisms through which CHD8 leads to these diseases. In summary, our results suggest that ASD share deregulated pathways and revealed that SHEDs represent an alternative cell source to be used in the understanding of the biological mechanisms involved in the etiology of ASD. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/22213401 DOI: https://doi.org/10.1002/ana.22673  Title(2012): A novel X-linked disorder with developmental delay and autistic features.  Genomic duplications that lead to autism and other human diseases are interesting pathological lesions since the underlying mechanism almost certainly involves dosage sensitive genes. We aim to understand a novel genomic disorder with profound phenotypic consequences, most notably global developmental delay, autism, psychosis, and anorexia nervosa. We evaluated the affected individuals, all maternally related, using childhood autism rating scale (CARS) and Vineland Adaptive scales, magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) brain, electroencephalography (EEG), electromyography (EMG), muscle biopsy, high-resolution molecular karyotype arrays, Giemsa banding (G-banding) and fluorescent in situ hybridization (FISH) experiments, mitochondrial DNA (mtDNA) sequencing, X-chromosome inactivation study, global gene expression analysis on Epstein-Barr virus (EBV)-transformed lymphoblasts, and quantitative reverse-transcription polymerase chain reaction (qRT-PCR). We have identified a novel Xq12-q13.3 duplication in an extended family. Clinically normal mothers were completely skewed in favor of the normal chromosome X. Global transcriptional profiling of affected individuals and controls revealed significant alterations of genes and pathways in a pattern consistent with previous microarray studies of autism spectrum disorder patients. Moreover, expression analysis revealed copy number-dependent increased messenger RNA (mRNA) levels in affected patients compared to control individuals. A subset of differentially expressed genes was validated using qRT-PCR. Xq12-q13.3 duplication is a novel global developmental delay and autism-predisposing chromosomal aberration; pathogenesis of which may be mediated by increased dosage of genes contained in the duplication, including NLGN3, OPHN1, AR, EFNB1, TAF1, GJB1, and MED12. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/21465671 DOI: https://doi.org/10.1002/aur.191  Title(2011): Male predominance in autism: neuroendocrine influences on arousal and social anxiety.  We offer a neurobiologic theory based on animal work that helps account for the conspicuous male predominance in autism spectrum disorders (ASD). In young male animals, testosterone (TST) binds to androgen receptors (AR) in brainstem neurons responsible for enhancing brain arousal. As a consequence, arousal-related neurotransmitters bombard the amygdala hypersensitized by TST acting though AR. Arousal-related inputs are known to prime amygdaloid mechanisms for fear and anxiety, with resultant social avoidance. We hypothesize that similar mechanisms contribute to autism's male predominance and to its defining impaired social skills. The theory rests on two key interacting factors: the molecular effects of TST in genetically vulnerable boys in combination with environmental stresses they experienced in utero, neonatally, or during the first years. We postulate that higher TST levels and, therefore, higher amounts of arousal-related inputs to the amygdala sensitize these genetically vulnerable male infants to very early stresses. In sharp contrast to boys, girls not only do not have high levels of TST-facilitated arousal-causing inputs to the amygdala but they also enjoy the protection afforded by estrogenic hormones, oxytocin, and the oxytocin receptor. This theory suggests that novel technologies applied to the molecular endocrinology of TST's actions through AR will offer new avenues of enquiry into ASD. Since the high male preponderance in autism is important yet understudied, we offer our theory, which is based on detailed neurobehavioral research with animals, to stimulate basic and clinical research in animals and humans and hopefully help develop novel more effective medical treatments for autism. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/20425835 DOI: https://doi.org/10.1002/ajmg.a.33352  Title(2010): FMR1 gene expansion, large deletion of Xp, and skewed X-inactivation in a girl with mental retardation and autism.  We describe a girl with mild facial anomalies, mild mental retardation, and atypical autism with a remarkable behavioral phenotype of persistent anger, aggression, and dysphoria. The occurrence of late-onset tremor and premature ovarian failure in the maternal branch of the family pointed to a possible defect in the FMR1 gene. Indeed, the patient carried a full FMR1 mutation. Unexpectedly, both alleles of the gene were almost completely methylated. Cytogenetic examination of the patient revealed in addition a large de novo deletion in band Xp22 on one of her X chromosomes. The deletion was fine mapped using oligonucleotide array CGH, and its breakpoints were localized using sequencing. The size of the deletion was about 17.4 Mb, and it contained more than 90 protein-coding genes. Microsatellite analysis indicated paternal origin of the aberrant chromosome. The large rearrangement was the most probable cause of the X-inactivation skewing, thus explaining the methylation of not only the expanded (maternal) but also the normal (paternal) FMR1 alleles. This pattern of skewed X-inactivation was confirmed using the analysis of methylation at the AR locus. The relatively mild phenotype of the patient resulted most likely from unmasking of the FMR1 defect. Although the deleted region contained many important genes, the phenotypic contribution of the rearranged X chromosome was probably limited by its almost complete inactivation. However, reduced dose of several genes escaping X-inactivation might also play a role in the phenotype of the patient. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/19167832 DOI: https://doi.org/10.1016/j.psyneuen.2008.12.007  Title(2009): Possible association between the androgen receptor gene and autism spectrum disorder.  Autism is a highly heritable disorder but the specific genes involved remain largely unknown. The higher prevalence of autism in men than in women, in conjunction with a number of other observations, has led to the suggestion that prenatal brain exposure to androgens may be of importance for the development of this condition. Prompted by this hypothesis, we investigated the potential influence of variation in the androgen receptor (AR) gene on the susceptibility for autism. To this end, 267 subjects with autism spectrum disorder and 617 controls were genotyped for three polymorphisms in exon 1 of the AR gene: the CAG repeat, the GGN repeat and the rs6152 SNP. In addition, parents and affected siblings were genotyped for 118 and 32 of the cases, respectively. Case-control comparisons revealed higher prevalence of short CAG alleles as well as of the A allele of the rs6152 SNP in female cases than in controls, but revealed no significant differences with respect to the GGN repeat. Analysis of the 118 families using transmission disequilibrium test, on the other hand, suggested an association with the GGN polymorphism, the rare 20-repeat allele being undertransmitted to male cases and the 23-repeat allele being overtransmitted to female cases. Sequencing of the AR gene in 46 patients revealed no mutations or rare variants. The results lend some support for an influence of the studied polymorphisms on the susceptibility for autism, but argue against the possibility that mutations in the AR gene are common in subjects with this condition. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/19132145 DOI: https://doi.org/10.1002/aur.24  Title(2008): MECP2 promoter methylation and X chromosome inactivation in autism.  Epigenetic mechanisms have been proposed to play a role in the etiology of autism. This hypothesis is supported by the discovery of increased MECP2 promoter methylation associated with decreased MeCP2 protein expression in autism male brain. To further understand the influence of female X chromosome inactivation (XCI) and neighboring methylation patterns on aberrant MECP2 promoter methylation in autism, multiple methylation analyses were peformed on brain and blood samples from individuals with autism. Bisulfite sequencing analyses of a region 0.6 kb upstream of MECP2 in brain DNA samples revealed an abrupt transition from a highly methylated region in both sexes to a region unmethylated in males and subject to XCI in females. Chromatin immunoprecipitation analysis demonstrated that the CCTC-binding factor (CTCF) bound to this transition region in neuronal cells, consistent with a chromatin boundary at the methylation transition. Male autism brain DNA samples displayed a slight increase in methylation in this transition region, suggesting a possible aberrant spreading of methylation into the MECP2 promoter in autism males across this boundary element. In addition, autistic female brain DNA samples showed evidence for aberrant MECP2 promoter methylation as an increase in the number of bisulfite sequenced clones with undefined XCI status for MECP2 but not androgen receptor (AR). To further investigate the specificity of MECP2 methylation alterations in autism, blood DNA samples from females and mothers of males with autism were also examined for XCI skewing at AR, but no significant increase in XCI skewing was observed compared to controls. These results suggest that the aberrant MECP2 methylation in autism brain DNA samples is due to locus-specific rather than global X chromosome methylation changes. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/16167093 DOI: https://doi.org/10.1007/s10803-005-0011-z  Title(2005): Brief report: non-random X chromosome inactivation in females with autism.  Autism is a heterogeneous neurodevelopmental disorder with a 3-4 times higher sex ratio in males than females. X chromosome genes may contribute to this higher sex ratio through unusual skewing of X chromosome inactivation. We studied X chromosome skewness in 30 females with classical autism and 35 similarly aged unaffected female siblings as controls using the polymorphic androgen receptor (AR) gene. Significantly, increased X chromosome skewness (e.g., >80:20%) was detected in our autism group (33%) compared to unaffected females (11%). X chromosome skewness was also seen in 50% of the mothers with autistic daughters. No mutation was seen in the promoter region of the XIST gene reported to be involved in X chromosome inactivation in our subjects. X chromosome skewness has been reported in female carriers of other neurological disorders such as X-linked mental retardation, adrenoleukodystrophy and Rett syndrome. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/35563368 DOI: https://doi.org/10.3390/ijms23094978  Title(2022): Androgens Upregulate Pathogen-Induced Placental Innate Immune Response.  Group B Streptococcus (GBS) is a leading cause of placental infection, termed chorioamnionitis. Chorioamnionitis is associated with an increased risk of neurobehavioral impairments, such as autism spectrum disorders, which are more prominent in males than in female offspring. In a pre-clinical model of chorioamnionitis, a greater inflammatory response was observed in placenta associated with male rather than female fetuses, correlating with the severity of subsequent neurobehavioral impairments. The reason for this sex difference is not understood. Our hypothesis is that androgens upregulate the placental innate immune response in male fetuses. Lewis dams were injected daily from gestational day (G) 18 to 21 with corn oil (vehicle) or an androgen receptor antagonist (flutamide). On G 19, dams were injected with saline (control) or GBS. Maternal, fetal sera and placentas were collected for protein assays and in situ analyses. Our results showed that while flutamide alone had no effect, a decrease in placental concentration of pro-inflammatory cytokines and infiltration of polymorphonuclear cells was observed in flutamide/infected compared to vehicle/infected groups. These results show that androgens upregulate the placental innate immune response and thus may contribute to the skewed sex ratio towards males observed in several developmental impairments resulting from perinatal infection/inflammation. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/33535392 DOI: https://doi.org/10.3390/diseases9010013  Title(2021): Testosterone/Epitestosterone Ratios-Further Hints to Explain Hyperandrogenemia in Children with Autism.  Epitestosterone [E] has for a long time been considered as a biologically inactive androgen. However, recently a distinct antiandrogenic activity of this naturally occurring endogenous epimer of Testosterone has been demonstrated. Especially the ratios of testosterone/epitestosterone (T/E) seem to be key as inhibition of epitestosterone on androgen activity was postulated. As in autism, a higher androgen activity was implied. We, therefore, suggested higher levels of T/E ratios of children with autism versus children with typical development. Urine probes of 22 girls with autism (BMI 18.7 ± 4.3; average age 12.3 ± 3.8 years) and a sample of 51 controls (BMI 17.0 ± 2.6; average age 11.9 ± 4 years), as well as 61 boys with autism (BMI 17.04 ± 2. average age 11.9 ± 2.5 years) and 61 control boys (BMI 17.0 ± 2.6; average age 11.1 ± 3.0 years), were analyzed with gas chromatography mass spectrometry. The average T/E ratio of all boys with autism was 2.5 ± 1.8 versus 2.4 ± 1.3 in boys with typical development, respectively. No significant difference between boys with autism versus boys with typical development could be detected (p = 0.977). In girls with autism, the average T/E ratio was 1.4 ± 0.9 versus 2.0 ± 1.4 in girls with typical development, whereby a significant difference could be detected (p = 0.0285). Further, polynomial analysis of the third degree were conducted, showing a dependence from age with reasonable coefficients of determination (0.075 2 < 0.22, all samples). As encompassing steroid hormone analysis are expensive and work-intensive, we hoped to find an easily applicable biomarker to support diagnostics in autism. However, as a relatively small sample of only 22 girls with autism were analyzed and menstrual cycle and pubertal status were only partly controllable through the matching of BMI and age, the question arises if it was an incidental finding. Nevertheless, one suggestion might be that epitestosterone has the effect of a competitive inhibition on the androgen receptor, which would probably help to explain the higher prevalence of autism in boys as compared to girls. Presumably, as no significant difference was detected in boys, this effect might not be as relevant from a steroid hormone perspective, and other effects such as altered 17/20-hydroxylase activity as previously shown in boys and girls with autism seem to have more relevance. Analysis of larger samples, including plenty of metabolites and enzymatic cascades, as well as the role of backdoor pathway activity of androgen synthesis of girls with autism, are demanded in order to validate current findings of altered steroid hormones in autism. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/30319350 DOI: https://doi.org/10.3389/fnmol.2018.00337  Title(2018): Sex Hormones Regulate SHANK Expression.  Autism spectrum disorders (ASD) have a higher prevalence in male individuals compared to females, with a ratio of affected boys compared to girls of 4:1 for ASD and 11:1 for Asperger syndrome. Mutations in the SHANK genes (comprising SHANK1, SHANK2 and SHANK3) coding for postsynaptic scaffolding proteins have been tightly associated with ASD. As early brain development is strongly influenced by sex hormones, we investigated the effect of dihydrotestosterone (DHT) and 17β-estradiol on SHANK expression in a human neuroblastoma cell model. Both sex hormones had a significant impact on the expression of all three SHANK genes, which could be effectively blocked by androgen and estrogen receptor antagonists. In neuron-specific androgen receptor knock-out mice (Ar NesCre), we found a nominal significant reduction of all Shank genes at postnatal day 7.5 in the cortex. In the developing cortex of wild-type (WT) CD1 mice, a sex-differential protein expression was identified for all Shanks at embryonic day 17.5 and postnatal day 7.5 with significantly higher protein levels in male compared to female mice. Together, we could show that SHANK expression is influenced by sex hormones leading to a sex-differential expression, thus providing novel insights into the sex bias in ASD. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/29428674 DOI: https://doi.org/10.1016/j.biopsych.2018.01.002  Title(2018): Genes and Pathways Regulated by Androgens in Human Neural Cells, Potential Candidates for the Male Excess in Autism Spectrum Disorder.  Prenatal exposure to androgens during brain development in male individuals may participate to increase their susceptibility to develop neurodevelopmental disorders such as autism spectrum disorder (ASD) and intellectual disability. However, little is known about the action of androgens in human neural cells. We used human neural stem cells differentiated from embryonic stem cells to investigate targets of androgens. RNA sequencing revealed that treatment with dihydrotestosterone (DHT) leads to subtle but significant changes in the expression of about 200 genes, encoding proteins of extracellular matrix or involved in signal transduction of growth factors (e.g., insulin/insulin growth factor 1). We showed that the most differentially expressed genes (DEGs), RGCC, RNF144B, NRCAM, TRIM22, FAM107A, IGFBP5, and LAMA2, are reproducibly regulated by different androgens in different genetic backgrounds. We showed, by overexpressing the androgen receptor in neuroblastoma cells SH-SY5Y or knocking it down in human neural stem cells, that this regulation involves the androgen receptor. A chromatin immunoprecipitation combined with direct sequencing analysis identified androgen receptor-bound sequences in nearly half of the DHT-DEGs and in numerous other genes. DHT-DEGs appear enriched in genes involved in ASD (ASXL3, NLGN4X, etc.), associated with ASD (NRCAM), or differentially expressed in patients with ASD (FAM107A, IGFBP5). Androgens increase human neural stem cell proliferation and survival in nutrient-deprived culture conditions, with no detectable effect on regulation of neurite outgrowth. We characterized androgen action in neural progenitor cells, identifying DHT-DEGs that appear to be enriched in genes related to ASD. We also showed that androgens increase proliferation of neuronal precursors and protect them from death during their differentiation in nutrient-deprived conditions. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/28204507 DOI: https://doi.org/10.1093/hmg/ddx055  Title(2017): Foxp1 expression is essential for sex-specific murine neonatal ultrasonic vocalization.  Autism and speech and language deficits are predominantly found in boys, however the causative mechanisms for this sex bias are unknown. Human FOXP1 is associated with autism, intellectual disability and speech and language deficits. Its closely related family member FOXP2 is involved in speech and language disorder and Foxp2 deficient mice have demonstrated an absence of ultrasonic vocalizations (USVs). Since Foxp1 and Foxp2 form heterodimers for transcriptional regulation, we investigated USV in neonatal brain-specific Foxp1 KO mice. Foxp1 KO pups had strongly reduced USV and lacked the sex-specific call rate from WT pups, indicating that Foxp1 is essential for normal USV. As expression differences of Foxp1 or Foxp2 could explain the sex-dimorphic vocalization in WT animals, we quantified both proteins in the striatum and cortex at P7.5 and detected a sex-specific expression of Foxp2 in the striatum. We further analyzed Foxp1 and Foxp2 expression in the striatum and cortex of CD1 mice at different embryonic and postnatal stages and observed sex differences in both genes at E17.5 and P7.5. Sex hormones, especially androgens are known to play a crucial role in the sexual differentiation of vocalizations in many vertebrates. We show that Foxp1 and the androgen receptor are co-expressed in striatal medium spiny neurons and that brain-specific androgen receptor KO (ArNesCre) mice exhibit reduced Foxp1 expression in the striatum at E17.5 and P7.5 and an increased Foxp2 level in the cortex at P7.5. Thus, androgens may contribute to sex-specific differences in Foxp1 and Foxp2 expression and USV. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/26910733 DOI: https://doi.org/10.1371/journal.pone.0149657  Title(2016): Testosterone and Androgen Receptor Sensitivity in Relation to Hyperactivity Symptoms in Boys with Autism Spectrum Disorders.  Autism spectrum disorders (ASD) and hyperactivity symptoms exhibit an incidence that is male-biased. Thus androgen activity can be considered a plausible biological risk factor for these disorders. However, there is insufficient information about the association between increased androgen activity and hyperactivity symptoms in children with ASD. In the present study, the relationship between parameters of androgenicity (plasmatic testosterone levels and androgen receptor sensitivity) and hyperactivity in 60 boys (age 3-15) with ASD is investigated. Given well documented differences in parent and trained examiners ratings of symptom severity, we employed a standardized parent`s questionnaire (Nisonger Child Behavior Rating Form) as well as a direct examiner`s rating (Autism diagnostic observation schedule) for assessment of hyperactivity symptoms. Although it was found there was no significant association between actual plasmatic testosterone levels and hyperactivity symptoms, the number of CAG triplets was significantly negatively correlated with hyperactivity symptoms (R2 = 0.118, p = 0.007) in the sample, indicating increased androgen receptor sensitivity in association with hyperactivity symptoms. Direct trained examiner´s assessment appeared to be a relevant method for evaluating of behavioral problems in the investigation of biological underpinnings of these problems in our study. A potential ASD subtype characterized by increased rates of hyperactivity symptoms might have distinct etiopathogenesis and require a specific behavioral and pharmacological approach. We propose an increase of androgen receptor sensitivity as a biomarker for a specific ASD subtype accompanied with hyperactivity symptoms. Findings are discussed in terms of their implications for practice and future research. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/26781567 DOI: https://doi.org/10.1007/s11682-015-9504-3  Title(2017): Developmental neurogenetics and multimodal neuroimaging of sex differences in autism.  Examining sex differences in the brain has been historically contentious but is nonetheless important for advancing mental health for both girls and boys. Unfortunately, females in biomedical research remain underrepresented in most mental health conditions including autism spectrum disorders (ASD), even though equal inclusion of females would improve treatment for girls and yield benefits to boys. This review examines sex differences in the relationship between neuroanatomy and neurogenetics of ASD. Recent findings reveal that girls diagnosed with ASD exhibit more intellectual and behavioral problems compared to their male counterparts, suggesting that girls may be less likely diagnosed in the absence of such problems or that they require a higher mutational load to meet the diagnostic criteria. Thus far, the female biased effect of chromosome 4, 5p15.33, 8p, 9p24.1, 11p12-13, 15q, and Xp22.3 and the male biased effect of 1p31.3, 5q12.3, 7q, 9q33.3, 11q13.4, 13q33.3, 16p11.2, 17q11-21, Xp22.33/Yp11.31, DRD1, NLGN3, MAOA, and SHANK1 deletion have been discovered in ASD. The SNPs of genes such as RYR2, UPP2, and the androgen receptor gene have been shown to have sex-biasing factors in both girls and boys diagnosed with ASD. These sex-related genetic factors may drive sex differences in the neuroanatomy of these girls and boys, including abnormal enlargement in temporal gray and white matter volumes, and atypical reduction in cerebellar gray matter volumes and corpus callosum fibers projecting to the anterior frontal cortex in ASD girls relative to boys. Such factors may also be responsible for the attenuation of brain sexual differentiation in adult men and women with ASD; however, much remains to be uncovered or replicated. Future research should leverage further the association between neuroanatomy and genetics in girls for an integrated and interdisciplinary understanding of ASD. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/24865607 DOI: https://doi.org/10.1111/j.2047-2927.2014.00229.x  Title(2014): Neuropsychology and brain morphology in Klinefelter syndrome - the impact of genetics.  Klinefelter syndrome (KS, 47,XXY) is associated with increased psychiatric morbidity and cognitive disabilities, although the neuropsychological phenotype shows great variability. Androgen receptor polymorphism (CAG repeat length), skewed X-chromosome inactivation and parent-of-origin of the extra X-chromosome have been suggested to influence cognitive function and psychological traits. These issues have not been clarified for KS patients. We studied X-chromosome inactivation pattern, CAG repeat length and parent-of-origin in relation to educational and cohabitation status, personality and autism traits, psychological distress, cognitive function and brain volumes in 73 KS patients and 73 controls. Grey matter (GM) volume of left insula was significantly decreased in KS patients with skewed X-inactivation (z = 5.78) and we observed a borderline significant difference in global brain matter volume where KS patients with skewed X-chromosome inactivation tended to have smaller brains. Skewed X-inactivation, CAG repeat length and parent-of-origin were not correlated with educational and marital status, personality traits, autism traits, and psychological distress, prevalence of depression and anxiety or cognitive function. Interestingly our results regarding brain volumes indicate that X-inactivation has an influence on GM volume in left insula and might also be related to global GM volume, indicating a possible effect of X-linked genes on the development of GM volume in KS patient. Skewed X-inactivation, CAG repeat length and parent-of-origin have no impact on the neuropsychological phenotype in KS (http://www.clinicaltrials.gov (Clinical trial NCT00999310)). |
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| Url: https://pubmed.ncbi.nlm.nih.gov/22738402 DOI: https://doi.org/10.1186/2040-2392-3-5  Title(2012): High-functioning autism spectrum disorder and fragile X syndrome: report of two affected sisters.  Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability (ID), as well as the most frequent monogenic cause of autism spectrum disorder (ASD). Men with FXS exhibit ID, often associated with autistics features, whereas women heterozygous for the full mutation are typically less severely affected; about half have a normal or borderline intelligence quotient (IQ). Previous findings have shown a strong association between ID and ASD in both men and women with FXS. We describe here the case of two sisters with ASD and FXS but without ID. One of the sisters presented with high-functioning autism, the other one with pervasive developmental disorder not otherwise specified and low normal IQ. The methylation status of the mutated FMR1 alleles was examined by Southern blot and methylation-sensitive polymerase chain reaction. The X-chromosome inactivation was determined by analyzing the methylation status of the androgen receptor at Xq12. Both sisters carried a full mutation in the FMR1 gene, with complete methylation and random X chromosome inactivation. We present the phenotype of the two sisters and other family members. These findings suggest that autistic behaviors and cognitive impairment can manifest as independent traits in FXS. Mutations in FMR1, known to cause syndromic autism, may also contribute to the etiology of high-functioning, non-syndromic ASD, particularly in women. Thus, screening for FXS in patients with ASD should not be limited to those with comorbid ID. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/21035791 DOI: https://doi.org/10.1016/j.biopsych.2010.08.034  Title(2010): The parent-of-origin of the extra X chromosome may differentially affect psychopathology in Klinefelter syndrome.  Several genetic mechanisms have been proposed for the variability of the Klinefelter syndrome (KS) phenotype such as the parent-of-origin of the extra X chromosome. Parent-of-origin effects on behavior in KS can possibly provide insights into X-linked imprinting effects on psychopathology that may be extrapolated to other populations. Here, we investigated whether the parent-of-origin of the supernumerary X chromosome influences autistic and schizotypal symptom profiles in KS. Parent-of-origin of the X chromosome was determined through analysis of the polymorphic CAG tandem repeat of the androgen receptor gene. Autistic traits (Autism Diagnostic Interview-Revised) were measured in a younger KS sample (n = 33) with KS and schizotypal traits (Schizotypal Personality Questionnaire) were assessed in an older KS sample (n = 43). Scale scores on these questionnaires were entered in statistical analyses to test parent-of-origin effects. The results show that parent-of-origin of the X chromosome is reflected in autistic and schizotypal symptomatology. Differences were shown in the degree of both schizotypal and autistic symptoms between the parent-of-origin groups. Furthermore, the parent-of-origin could be correctly discriminated in more than 90% of subjects through Autism Diagnostic Interview-Revised scales and in around 80% of subjects through Schizotypal Personality Questionnaire scales. These findings point to parent-of-origin effects on psychopathology in KS and indicate that imprinted X chromosomal genes may have differential effects on autistic and schizotypal traits. Further exploration of imprinting effects on psychopathology in KS is needed to confirm and expand on our findings. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/20631003 DOI: https://doi.org/10.1210/en.2010-0041  Title(2010): Minireview: Organizational hypothesis: instances of the fingerpost.  There is now compelling evidence that the ratio of the length of the second digit divided by the length of the fourth digit (2D:4D) is affected by prenatal androgens in humans. This ratio is greater in females than males from fetal life through adulthood, correlates with polymorphism in the androgen receptor gene in men, is feminine in XY androgen insensitivity syndrome, and masculinized in congenital adrenal hyperplasia. Using 2D:4D as a correlate, researchers have found evidence that prenatal androgens affect many sexually differentiated human behaviors, including sexual orientation in women (but not in men), attention deficit disorder, autism, eating disorders, aggression, and risk-taking. In each case, lower 2D:4D, indicative of greater prenatal androgen stimulation, is associated with behavior more commonly displayed by males than females. The correlation between 2D:4D and prenatal androgen stimulation is too imperfect to accurately predict the phenotype of a particular individual, even in terms of sex. However, digit ratio is the best available retrospective marker of average differences in prenatal androgen stimulation between groups of people, and/or correlations of prenatal androgen stimulation with particular behaviors and characteristics within a group. Thus digit ratios offer a valid test of the organizational hypothesis that androgens act early in life to masculinize various human behaviors. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/15091318 DOI: https://doi.org/10.1097/00041444-200403000-00010  Title(2004): Mutation scanning of the androgen receptor gene in patients with psychiatric disorders reveals highly conserved variants in alcoholic and phobia patients.  Sex steroids exert potent effects on mood and mental state in humans. They may contribute to the risk of psychiatric disorders. To investigate this hypothesis, coding and splice junction sequences of the androgen receptor gene were scanned in genomic DNA samples to search for variants affecting protein structure and expression (VAPSEs). Ninety-six schizophrenics, along with pilot samples of patients with bipolar disorder, attention-deficit hyperactivity disorder, alcoholism and autism were analyzed with DOVAM-S, a robotically enhanced, optimized form of single-strand conformation polymorphism analysis. A total of 669 kb of genomic sequence was analyzed. Two VAPSEs were identified: R726L was found in one of 17 scanned alcoholics, and P516S, a novel VAPSE, was identified in one of three phobia patients. There were no length trends of the CAG triplets associated with schizophrenia. R726L and P516S occur at highly conserved amino acids. Further study is required to assess whether these VAPSEs contribute to the risk of alcoholism or phobia or other diseases. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/12966522 DOI: https://doi.org/10.1002/ajmg.a.20320  Title(2003): Rett syndrome in a 47,XXX patient with a de novo MECP2 mutation.  Rett syndrome is caused by mutation in MECP2, a gene located on Xq28 and subject to X-inactivation. MECP2 encodes methyl CpG-binding protein 2, a widely expressed transcriptional repressor of methylated DNA. Mutations in MECP2 are primarily de novo events in the male germ line and thus lead to an excess of affected females. Here we report the identification of a unique 47,XXX girl with relatively mild atypical Rett syndrome leading initially to a diagnosis of infantile autism with regression. Mutation analysis of the MECP2 gene identified a de novo MECP2 mutation, L100V. Examination of a panel of X-linked microsatellite markers indicated that her supernumerary X chromosome is maternally derived. X-inactivation patterns were determined by analysis of methylation of the androgen receptor locus, and indicated preferential inactivation of her paternal allele. The parental origin of her MECP2 mutation could not be determined because she was uninformative for intronic polymorphisms flanking her mutation. This is the first reported case of sex chromosome trisomy and MECP2 mutation in a female, and it illustrates the importance of allele dosage on the severity of Rett syndrome phenotype. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/37396155 DOI: https://doi.org/10.1016/j.jtcme.2023.02.005  Title(2023): Hydroalcoholic extract of Passiflora incarnata improves the autistic-like behavior and neuronal damage in a valproic acid-induced rat model of autism.  Experimental autism in rodents can be caused by prenatal valproic acid (VPA) exposure. Some diseases, such as attention-deficit hyperactivity disorder (ADHD), insomnia, opiate withdrawal, and generalized anxiety disorder can be treated by consuming Passiflora incarnata, due to the possession of bioactive compounds like alkaloids, phenols, and flavonoids. The present study aims to investigate the role of the hydroalcoholic extract of Passiflora incarnata in behavioral and oxidative stress aberrations induced by VPA. On the gestational day (GD), 12.5, pregnant Wistar rats received VPA (600 mg/kg subcutaneously). Male pups were treated with the extract (30,100, and 300 mg/kg) from postnatal day 35 to the end of the experiment, and underwent behavioral testing to evaluate locomotion, repetitive, and stereotyped movements, anxiety, and social and cognitive behaviors. After behavioral testing, the blood sample was taken from the left ventricle to determine serum catalase (CAT), superoxide dismutase (SOD), malondialdehyde (MDA), and total antioxidant capacity (TAC). Then the animals were euthanized and their brains were taken out for histological assays of the prefrontal cortex (PFC) and CA1 hippocampus with hematoxylin/eosin. The total phenol and flavonoid content and antioxidant activity of the extract were also measured. A significant improvement was observed in behavioral disturbances, particularly with 300 mg/kg of Passiflora. Moreover, the formation of oxidative stress markers significantly decreased at this dose. The extract also reduced the percentage of damaged cells in the CA1 and PFC. The results indicated that Passiflora extract could ameliorate VPA-induced behavioral aberrations possibly due to the antioxidant actions of its bioactive compounds. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/37357844 DOI: https://doi.org/10.1002/tox.23876  Title(2023): Syringic acid alleviates valproic acid induced autism via activation of p38 mitogen-activated protein kinase: Possible molecular approach.  Autism spectrum disorder (ASD) is a multifactorial neurodevelopmental disorder characterized by restrictive and repetitive behavior followed by impairment in social, verbal, and non-verbal interaction and communication. Valproic acid (VPA) is a well-known anti-epileptic drug, but its prenatal exposure to animals causes social impairment, neurotransmitters imbalance, and neuroinflammation with ASD-like phenotypes. Syringic acid (SA) is a polyphenolic compound with anti-inflammatory, anti-apoptotic, antioxidant, and neuromodulator activity. The purpose of study was to investigate the protective effect of Syringic acid (SA) in prenatal VPA-treated rats through behavioral, neuroinflammation, oxidative stress, neurotransmitters, neuronal integrity, and apoptotic marker. Single dose of VPA was administered 600 mg/kg, i.p. on a gestational day (GD) 12th and SA was administrated from PnD 26th to 54th at the dose of 25, 50, and 100 mg/kg, p.o. On PnD 56th behavioral parameters (Pain sensitivity, open field test, narrow beam walks test and social impairment test) were performed and all animals were sacrificed, and brain tissue was isolated for oxidative stress (GSH, CAT, and LPO), neuroinflammation (TNF-α and IL-6) and neurotransmitters (GABA and Glutamate), histopathology (H&E, Nissl), immunohistochemistry (p38 MAPK) analysis. Rat treated with SA dose-dependently prevented behavioral alteration, restored antioxidant enzymes, neurotransmitters level, decreased neuroinflammatory markers, and improved neuronal integrity. Furthermore, immunohistochemistry confirmed the reduced p38 MAPK marker expression by SA in VPA induced autistic behavior. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/37333916 DOI: https://doi.org/10.3389/fpsyt.2023.1209638  Title(2023): Shorter telomere length in children with autism spectrum disorder is associated with oxidative stress.  Autism spectrum disorder (ASD) is a highly heterogeneous neurodevelopmental disorder caused by a complex interaction between genetic and environmental risk factors. The balance between antioxidant capacity and oxidative stress (OS) induced free radicals may be crucial during the pathophysiological development of ASD. In this study, 96 children with ASD who met the diagnostic and statistical manual of mental disorders were collected, and the number of children in the typical development (TD) group was matched by 1:1. Digital PCR (dPCR) for telomere length (TL) expression in ASD in peripheral blood leukocytes. Urine levels of 8-hydroxy-2-deoxyguanosine (8-OHdG) content were measured by tandem triple quadrupole mass spectrometry and corrected by urinary creatinine levels. The levels of superoxide dismutase (SOD), catalase (CAT), and capacity (AOC) were detected by kits. The TL of the ASD group was shorter than the TD group (p p = 0.002). Both 8-OHdG content and SOD activity in the ASD group were significantly higher than those in the TD group (p p = 0.009; Multifactor: 2.22 (1.22, 4.00), p = 0.008) and reduced CAT activity (Monofactor: 2.31 (1.28, 4.17), p = 0.006; Multifactor: 2.31 (1.28, 4.18), p = 0.006) are risk factors for the development of ASD, while reduced 8-OHdG content (Monofactor: 0.29 (0.14, 0.60), p = 0.001; Multifactor: 0.27 (0.13, 0.57), p = 0.001) and reduced SOD activity (Monofactor: 0.55 (0.31, 0.98), p = 0.042; Multifactor: 0.54 (0.30, 0.98), p = 0.042) are protective factors for the development of ASD. In this study, TL and OS were significantly different between the ASD group and the TD group. As guanine-rich telomere sequences were likely damaged by oxygen free radicals, creating OS, which is a factor in the incidence and progression of ASDs. In conclusion, oxidative damage occurs in the bodies of children with ASD, which may lead to sustained disease progression and severe clinical manifestations. We assume that timely supplementation of antioxidants is very likely to be a potential treatment for early intervention in children with ASD. Identification and detection of OS-related biomarkers may contribute to early diagnosis and timely interventions in young patients with ASD. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/37242552 DOI: https://doi.org/10.3390/ph16050769  Title(2023): Canagliflozin Ameliorates Oxidative Stress and Autistic-like Features in Valproic-Acid-Induced Autism in Rats: Comparison with Aripiprazole Action.  Based on their proven anti-inflammatory and antioxidant effects, recent studies have examined the therapeutic potential of the sodium-glucose cotransporter 2 (SGLT2) inhibitors in neurodevelopmental disorders such as autism spectrum disorder (ASD). Therefore, the aim of this study is to assess the effects of subchronic systemic treatment with intraperitoneal (i.p.) canagliflozin (20, 50, and 100 mg/kg) compared to aripiprazole (ARP) (3 mg/g, i.p.) in a valproic acid (VPA)-induced rat model of autism. The behavioral characteristics of ASD, oxidative stress, and acetylcholinesterase (AChE) activity in rats with ASD-like behaviors, which were induced by prenatal exposure to VPA, were evaluated. The behavioral assessment methods used for this study were the open field test (OFT), the marble-burying test (MBT), and the nestlet-shredding test (NST) to examine their exploratory, anxiety, and compulsiveness-like actions, while the biochemical assessment used for this study was an ELISA colorimetric assay to measure ASD biomarker activity in the hippocampus, prefrontal cortex, and cerebellum. Rats that were pretreated with 100 mg/kg of canagliflozin displayed a significantly lower percentage of shredding (1.12 ± 0.6%, p p p p < 0.05) when compared with the VPA group (303 ± 140 s). Moreover, canagliflozin and ARP mitigated oxidative stress status by restoring levels of glutathione (GSH) and catalase (CAT) and increasing the levels of malondialdehyde (MDA) in all tested brain regions. The observed results propose repurposing of canagliflozin in the therapeutic management of ASD. However, further investigations are still required to verify the clinical relevance of canagliflozin in ASD. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/37084025 DOI: https://doi.org/10.1007/s12031-023-02110-5  Title(2023): GM1 Reduced the Symptoms of Autism Spectrum Disorder by Suppressing α-Syn Through Activating Autophagy.  Autism spectrum disorder (ASD) is a neurodevelopmental disorder that cannot be cured. The ASD rat model was developed in this study to demonstrate the role and mechanism of ganglioside GM1 (GM1). Rats were given valproic acid (VPA) to create the ASD rat model. The rats' behaviors were assessed using the Y-maze test, open-field test, three-chamber social interaction test, and Morris water maze test. Relative levels of glutathione (GSH), malondialdehyde (MDA), catalase (CAT), reactive oxygen species (ROS), and superoxide dismutase (SOD) were quantitated using relative kits. Nissl, TUNEL, immunofluorescent, and immunohistochemistry staining techniques were used. GM1 treatment improved the ASD model rats' behavior disorders, including locomotor activity and exploratory behavior, social interaction, learning and memory capacity, and repetitive behavior. Following GM1 injection, striatal neurons grew and apoptosis decreased. GM1 reduced the excessively elevated α-Syn in ASD by encouraging autophagy. The behavior disorder of ASD model rats was exacerbated by autophagy inhibition, which also increased α-Syn levels. By increasing autophagy, GM1 reduced α-Syn levels and, ultimately, improved behavioral abnormalities in ASD model rats. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/36930427 DOI: https://doi.org/10.1007/s12031-023-02111-4  Title(2023): Concurrent Assessment of Oxidative Stress and MT-ATP6 Gene Profiling to Facilitate Diagnosis of Autism Spectrum Disorder (ASD) in Tamil Nadu Population.  Autism spectrum disorder (ASD) is a neurodevelopmental disability that causes social impairment, debilitated verbal or nonverbal conversation, and restricted/repeated behavior. Recent research reveals that mitochondrial dysfunction and oxidative stress might play a pivotal role in ASD condition. The goal of this case-control study was to investigate oxidative stress and related alterations in ASD patients. In addition, the impact of mitochondrial DNA (mtDNA) mutations, particularly MT-ATP6, and its link with oxidative stress in ASD was studied. We found that ASD patient's plasma had lower superoxide dismutase (SOD) and higher catalase (CAT) activity, resulting in lower SOD/CAT ratio. MT-ATP6 mutation analysis revealed that four variations, 8865 G>A, 8684 C>T, 8697 G>A, and 8836 A>G, have a frequency of more than 10% with missense and synonymous (silent) mutations. It was observed that abnormalities in mitochondrial complexes (I, III, V) are more common in ASD, and it may have resulted in MT-ATP6 changes or vice versa. In conclusion, our findings authenticate that oxidative stress and genetics both have an equal and potential role behind ASD and we recommend to conduct more such concurrent research to understand their unique mechanism for better diagnosis and therapeutic for ASD. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/36642103 DOI: https://doi.org/10.1016/j.bbr.2023.114300  Title(2023): Preventive effect of quercetin-Loaded nanophytosome against autistic-like damage in maternal separation model: The possible role of Caspase-3, Bax/Bcl-2 and Nrf2.  The autism is an abnormality in the neuronal advance which starts before age 3 recognized by defective behaviors. This study aimed to make quercetin-loaded nanophytosomes (QNP) on behavioral deficits, cerebellar oxidative stress and apoptosis in an autistic-like model caused by maternal separation (MS). The newborn rats are randomly categorized into seven groups, including control, positive control, disease, and diseases treated with quercetin (10 and 40 mg/kg) and QNP (10 and 40 mg/kg). Pups exposed to MS for 3 h per day from postnatal days (PND) 1-9 showed behavioral impairment in adult rats compared to control group. The oral administration of quercetin and QNP was constantly started after the lactation period (21 postnatal days) for three weeks. Autistic-like behaviors, antioxidant parameters, and Nrf2, Bax/Bcl-2, and Caspase-3 expressions were surveyed in the cerebellum. Quercetin (40 mg/kg) treated improved some behavioral disorders. Also, the improvement of oxidative stress parameters, Nrf2 and apoptotic factors gene expression was observed in the cerebellum of quercetin (40 mg/kg) treated (p < 0.01). QNP treatment (10 and 40 mg/kg) significantly ameliorated anxiety-like behaviors, line crossing, and grooming index (p < 0.001), lipid peroxidation (p < 0.001), and increased catalase (CAT) (p < 0.001), superoxide dismutase (SOD) (p < 0.001), glutathione peroxidase (GPx) (p < 0.001) activity, and glutathione (GSH) levels (p < 0.05). Moreover, QNP significantly reduced Caspase-3 and Bax expression (p < 0.001), but increased Bcl-2, and Nrf2 expressions (p < 0.001). These findings indicated that QNP due to its high bioavailability was more effective than quercetin can be reduced autistic-like behavior, oxidative and apoptotic damages in the model of MS rats. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/36154275 DOI: https://doi.org/10.2217/epi-2022-0184  Title(2022): Genome-wide methylation analysis of post-mortem cerebellum samples supports the role of peroxisomes in autism spectrum disorder.  Aim: We tested the hypothesis that a subset of patients with autism spectrum disorder (ASD) contains candidate genes with high DNA methylation differences (effective values) that potentially affect one of the two alleles. Materials & methods: Genome-wide DNA methylation comparisons were made on cerebellum samples from 30 patients and 45 controls. Results: 12 genes with high effective values, including GSDMD, MMACHC, SLC6A5 and NKX6-2, implicated in ASD and other neuropsychiatric disorders were identified. Monoallelic promoter methylation and downregulation were observed for SERHL (serine hydrolase-like) and CAT (catalase) genes associated with peroxisome function. Conclusion: These data are consistent with the hypothesis implicating impaired peroxisome function/biogenesis for ASD. A similar approach holds promise for identifying rare epimutations in ASD and other complex disorders. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/35500829 DOI: https://doi.org/10.1016/j.jnutbio.2022.109034  Title(2022): Supplementation with selenium attenuates autism-like behaviors and improves oxidative stress, inflammation and related gene expression in an autism disease model.  Autism spectrum disorder (ASD) refers to a group of neurodevelopmental disorders. The etiology and pathological mechanisms of ASD are still unknown, and its prognosis is poor. This study investigated the effects of selenium (Se) supplementation on abnormal behavior and cognitive function in ASD model mice, as well as the potential action pathways. BTBR mice were randomly assigned to either a model group (BTBR group), a model selenium supplement group (BTBR+Se group), a normal control group (B6 group) or a normal selenium supplement group (B6+Se group). Sodium selenite, at a dosage of 1 mg/kg/day, was administered to the selenium supplementation groups by gavage. The mice in the BTBR group and the B6 group received the same amount of 0.9% saline by gavage. After 4 weeks of continuous intervention, the social functions and cognitive behaviors of the mice and the selenium concentration in hippocampal tissue were assessed. Hippocampal tissue structures were observed. Changes in neurotransmitter levels, oxidative stress and neuroinflammatory indicators were detected. SelP protein expression was significantly lower in hippocampal tissue from BTBR mice than in hippocampal tissue from B6 mice. The administration of sodium selenite in BTBR mice: (1) increased the expression of SelP; (2) attenuated spatial learning, memory impairment and improved social behaviors; (3) changed the serum levels of 5-HT, DA and Glu; (4) decreased the levels of inflammatory cytokines IL-6, IL-1β, and TNF-α in serum and hippocampal tissue; (5) reduced the ROS and MDA contents and significantly increased SOD activity, CAT activity, GSH-px activity, and antioxidant GSH levels; and (6) protected against neuronal loss in the hippocampus. Se supplementation significantly improved the social functioning, repetitive stereotyped behavior and cognitive function in BTBR mice. Se may play a protective role in the hippocampus of BTBR mice by regulating neurotransmitter levels, reducing oxidative stress, alleviating neuroinflammation and rescuing neural cell damage. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/35334937 DOI: https://doi.org/10.3390/nu14061280  Title(2022): Therapeutic Effects of a Novel Form of Biotin on Propionic Acid-Induced Autistic Features in Rats.  Magnesium biotinate (MgB) is a novel biotin complex with superior absorption and anti-inflammatory effects in the brain than D-Biotin. This study aimed to investigate the impact of different doses of MgB on social behavior deficits, learning and memory alteration, and inflammatory markers in propionic acid (PPA)-exposed rats. In this case, 35 Wistar rats (3 weeks old) were distributed into five groups: 1, Control; 2, PPA treated group; 3, PPA+MgBI (10 mg, HED); 4, PPA+MgBII (100 mg, HED); 5, PPA+MgBIII (500 mg, HED). PPA was given subcutaneously at 500 mg/kg/day for five days, followed by MgB for two weeks. PPA-exposed rats showed poor sociability and a high level of anxiety-like behaviors and cognitive impairments (p < 0.001). In a dose-dependent manner, behavioral and learning-memory disorders were significantly improved by MgB supplementation (p < 0.05). PPA decreased both the numbers and the sizes of Purkinje cells in the cerebellum. However, MgB administration increased the sizes and the densities of Purkinje cells. MgB improved the brain and serum Mg, biotin, serotonin, and dopamine concentrations, as well as antioxidant enzymes (CAT, SOD, GPx, and GSH) (p < 0.05). In addition, MgB treatment significantly regulated the neurotoxicity-related cytokines and neurotransmission-related markers. For instance, MgB significantly decreased the expression level of TNF-α, IL-6, IL-17, CCL-3, CCL-5, and CXCL-16 in the brain, compared to the control group (p < 0.05). These data demonstrate that MgB may ameliorate dysfunctions in social behavior, learning and memory and reduce the oxidative stress and inflammation indexes of the brain in a rat model. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/35307911 DOI: https://doi.org/10.1002/jbt.23035  Title(2022): Sumac and gallic acid-loaded nanophytosomes ameliorate hippocampal oxidative stress via regulation of Nrf2/Keap1 pathway in autistic rats.  Autism spectrum disorders cover a range of neurodevelopmental disorders characterized by impairments in social interaction and cognitive deficits. Phenolic compound applications have been restricted due to their poor solubility, bioavailability, and low stability. This paper aimed to explore the neuroprotective effects of sumac and gallic acid-loaded nanophytosomes (GNP) on oxidative stress-induced cognitive impairment and Nrf2/Keap1 gene expression in the autism model. Valproic acid (VPA) was administered intraperitoneally at doses of 500 mg/kg to female rats during gestational 12.5 days (E12.5). The prenatal VPA-exposed rats were divided into five groups, including VPA, VPA treated with sumac, gallic acid (GA), sumac-loaded nanophytosome (SNP), and GNP at doses of 20 mg/kg for 4 weeks (n = 6). A novel object test was conducted and antioxidant parameters and Nrf2/Keap1gene expression were evaluated in the hippocampus. According to the obtained results, the rat model of autism exhibited recognition memory impairment. We observed an increase in glutathione peroxidase (GPx), glutathione reductase (GRx), superoxide dismutase (SOD), catalase (CAT) enzyme activity, total antioxidant capacity (TAC), and glutathione (GSH) levels. Furthermore, sumac and GNP improved recognition memory deficits and increased GPx, GRx, SOD, and CAT activities, GSH and TAC levels, and Nrf2/Keap1gene expression in the hippocampal area. Our results also suggested that SNP and GNP ameliorate VPA-induced learning and memory deficits more efficiently than sumac extract and pure GA by reducing oxidative stress, enhancing antioxidant enzyme activity, and Keap1/Nrf2 gene expression. The present study demonstrated that the utilization of SNP and GNP significantly improved recognition memory deficits. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/34298871 DOI: https://doi.org/10.3390/ijms22147251  Title(2021): Curcumin Potentiates α7 Nicotinic Acetylcholine Receptors and Alleviates Autistic-Like Social Deficits and Brain Oxidative Stress Status in Mice.  Autistic spectrum disorder (ASD) refers to a group of neurodevelopmental disorders characterized by impaired social interaction and cognitive deficit, restricted repetitive behaviors, altered immune responses, and imbalanced oxidative stress status. In recent years, there has been a growing interest in studying the role of nicotinic acetylcholine receptors (nAChRs), specifically α7-nAChRs, in the CNS. Influence of agonists for α7-nAChRs on the cognitive behavior, learning, and memory formation has been demonstrated in neuro-pathological condition such as ASD and attention-deficit hyperactivity disorder (ADHD). Curcumin (CUR), the active compound of the spice turmeric, has been shown to act as a positive allosteric modulator of α7-nAChRs. Here we hypothesize that CUR, acting through α7-nAChRs, influences the neuropathology of ASD. In patch clamp studies, fast inward currents activated by choline, a selective agonist of α7-nAChRs, were significantly potentiated by CUR. Moreover, choline induced enhancement of spontaneous inhibitory postsynaptic currents was markedly increased in the presence of CUR. Furthermore, CUR (25, 50, and 100 mg/kg, i.p.) ameliorated dose-dependent social deficits without affecting locomotor activity or anxiety-like behaviors of tested male Black and Tan BRachyury (BTBR) mice. In addition, CUR (50 and 100 mg/kg, i.p.) mitigated oxidative stress status by restoring the decreased levels of superoxide dismutase (SOD) and catalase (CAT) in the hippocampus and the cerebellum of treated mice. Collectively, the observed results indicate that CUR potentiates α7-nAChRs in native central nervous system neurons, mitigates disturbed oxidative stress, and alleviates ASD-like features in BTBR mice used as an idiopathic rodent model of ASD, and may represent a promising novel pharmacological strategy for ASD treatment. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/33335642 DOI: https://doi.org/10.1155/2020/4539891  Title(2020): In Vitro Modulation of Endogenous Antioxidant Enzyme Activities and Oxidative Stress in Autism Lymphoblastoid Cell Line (ALCL) by Stingless Bee Honey Treatment.  Autism has been associated with a low antioxidant defense mechanism, while honey has been known for decades for its antioxidant and healing properties. Determination of stingless bee honey (KH) effects on antioxidant enzyme activities and oxidative damage in Autism Lymphoblastoid Cell Line (ALCL) was performed. ALCL and its normal sibling pair (NALCL) were cultured in RPMI-1640 medium at 37°C and 5% CO2. ALCL was treated with 400 μg/mL KH (24 h), and oxidative stress marker, malondialdehyde (MDA), and antioxidant enzyme activities (catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD)) were measured via enzyme-linked immunosorbent assay (ELISA), while deoxyribonucleic acid (DNA) damage was determined via comet assay. Low SOD activity (p p p p p p < 0.05) in ALCL compared to untreated ALCL. CAT activity showed no significant difference between all three groups, while the MDA level showed no significant difference between treated and untreated ALCL. In conclusion, KH treatment significantly reduced the oxidative stress in ALCL by increasing the SOD and GPx antioxidant enzyme activities, while reducing the DNA damage. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/32994972 DOI: https://doi.org/10.1002/fsn3.1813  Title(2020): Antioxidant and hepatorenal protective effects of bee pollen fractions against propionic acid-induced autistic feature in rats.  In the brain, propionic acid (PA) can cross cell membranes and accumulate within cells, leading to intracellular acidification, which may alter neurotransmitter release (NT), communication between neurons, and behavior. Such elevation in levels of PA constitutes a neurodevelopmental metabolic disorder called propionic acidemia, which could clinically manifest as autism. The purpose of this study was to investigate the protective effects of different fractions of bee pollen (BP) on PA-induced autism in rats, and to evaluate their effects on the expression of liver and renal biomarkers. Groups of rats received treatments of different fractions of BP at a dose of 250 mg/kg of body weight/day for a period of 1 month. Normal control group I and group II were orally administered with phosphate-buffered saline and propionic acid, respectively, for 3 days. BP contains various health-promoting phenolic components. Different fractions of BP administered pre- and post-treatment with PA showed significant reduction in the levels of liver and renal biomarkers (p < .05). Also, a significant enhancement in the levels of glutathione S-transferase (GST), catalase CAT), and ascorbic acid (VIT C) was observed. Supplementation with BP significantly reduced biochemical changes in the liver, kidneys, and brain of rats with PA-induced toxicity. It exhibited protective effects against oxidative damage and reactive oxygen species produced by PA-induced adverse reactions in rats. Taken together, our study shows that BP possesses protective effects in PA-induced liver and kidney damage. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/31996222 DOI: https://doi.org/10.1186/s12989-020-0336-y  Title(2020): Effects of PM2.5 and gases exposure during prenatal and early-life on autism-like phenotypes in male rat offspring.  Epidemiological studies have reported associations between elevated air pollution and autism spectrum disorders (ASD). However, we hypothesized that exposure to air pollution that mimics real world scenarios, is a potential contributor to ASD. The exact etiology and molecular mechanisms underlying ASD are not well understood. Thus, we assessed whether changes in OXTR levels may be part of the mechanism linking PM2.5/gaseous pollutant exposure and ASD. The current in-vivo study investigated the effect of exposure to fine particulate matter (PM2.5) and gaseous pollutants on ASD using behavioral and molecular experiments. Four exposure groups of Wistar rats were included in this study: 1) particulate matter and gaseous pollutants exposed (PGE), 2) gaseous pollutants only exposed (GE), 3) autism-like model (ALM) with VPA induction, and 4) clean air exposed (CAE) as the control. Pregnant dams and male pups were exposed to air pollutants from embryonic day (E0) to postnatal day (PND21). The average ± SD concentrations of air pollutants were: PM2.5: 43.8 ± 21.1 μg/m3, CO: 13.5 ± 2.5 ppm, NO2: 0.341 ± 0.100 ppm, SO2: 0.275 ± 0.07 ppm, and O3: 0.135 ± 0.01 ppm. The OXTR protein level, catalase activity (CAT), and GSH concentrations in the ALM, PGE, and GE rats were lower than those in control group (CAE). However, the decrements in the GE rats were smaller than other groups. Also in behavioral assessments, the ALM, PGE, and GE rats demonstrated a repetitive /restricted behavior and poor social interaction, but the GE rats had weaker responses compared to other groups of rats. The PGE and GE rats showed similar trends in these tests compared to the VPA rats. This study suggested that exposure to ambient air pollution contributed to ASD and that OXTR protein may serve as part of the mechanism linking them. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/29782990 DOI: https://doi.org/10.1016/j.freeradbiomed.2018.05.070  Title(2018): A certain role of SOD/CAT imbalance in pathogenesis of autism spectrum disorders.  The real impact of reactive oxygen species, antioxidant enzymes, mitochondrial dysfunction and chronic inflammation on the development of autism spectrum disorders (ASD) remains unclear, and even controversial. In this study we compared the plasma levels of antioxidant enzymes and their cofactors, markers of oxidative damage, and the respiratory burst in peripheral blood polymorphonuclear leucocytes (PMNL) as surrogate marker of chronic inflammation obtained from 10 children (4-10 year old) who met DSM-5 criteria and their siblings. We demonstrated diminished superoxide dismutase (SOD) and enhanced catalase (CAT) activities resulting in a markedly decreased SOD/CAT ratio and enhanced carbonyl content in the plasma of ASD patients. A strong correlation was present between SOD and CAT activities in the control group, which was not noted in ASD patients. Moreover, in autistic patients, we observed negative correlation between SOD activity on one side, and carbonyl content in plasma, 8-Hydroxy-2-deoxyguanosin content in urine, and respiratory burst intensity in PMNL on the other side. At the same time, low SOD level in autistic children was positively correlated with the magnesium content in the packed RBCs, which might indicate the involvement of the mitochondrial MnSOD in ASD pathogenesis, and therefore the consequent partaking of mitochondrial dysfunction in the development of ASD. Altogether, these results indicate that decreased antioxidant capacity and increased oxidative stress in ASD patients may have functional consequence in terms of increased superoxide leakage, oxidative protein damage, chronic inflammatory response, and, finally, neuronal cell abnormal functioning or death. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/26991849 DOI: https://doi.org/10.1016/j.etap.2016.03.006  Title(2016): Plasma phthalate and bisphenol a levels and oxidant-antioxidant status in autistic children.  Phthalates and bisphenol A (BPA) are endocrine disruting chemicals (EDCs) that are suggested to exert neurotoxic effects. This study aimed to determine plasma phthalates and BPA levels along with oxidant/antioxidant status in autistic children [n=51; including 12 children were diagnosed with "Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS)]. Plasma levels of BPA, di (2-ethylhexyl)-phthalate (DEHP) and its main metabolite mono (2-ethylhexyl)-phthalate (MEHP); thiobarbituric acid reactive substance (TBARS) and carbonyl groups; erythrocyte glutathione peroxidase (GPx1), thioredoxin reductase (TrxR), catalase (CAT), superoxide dismutase (SOD) and glutathione reductase (GR) activities and glutathione (GSH) and selenium levels were measured. Plasma BPA levels of children with PDD-NOS were significantly higher than both classic autistic children and controls (n=50). Carbonyl, selenium concentrations and GPx1, SOD and GR activities were higher (p<0.05); CAT activity was markedly lower in study group. BPA exposure might be associated with PDD-NOS. Intracellular imbalance between oxidant and antioxidant status might facilitate its neurotoxicity. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/26215737 DOI: https://doi.org/10.1007/s00726-015-2057-3  Title(2015): Hypomorphic variants of cationic amino acid transporter 3 in males with autism spectrum disorders.  Cationic amino acid transporters (CATs) mediate the entry of L-type cationic amino acids (arginine, ornithine and lysine) into the cells including neurons. CAT-3, encoded by the SLC7A3 gene on chromosome X, is one of the three CATs present in the human genome, with selective expression in brain. SLC7A3 is highly intolerant to variation in humans, as attested by the low frequency of deleterious variants in available databases, but the impact on variants in this gene in humans remains undefined. In this study, we identified a missense variant in SLC7A3, encoding the CAT-3 cationic amino acid transporter, on chromosome X by exome sequencing in two brothers with autism spectrum disorder (ASD). We then sequenced the SLC7A3 coding sequence in 148 male patients with ASD and identified three additional rare missense variants in unrelated patients. Functional analyses of the mutant transporters showed that two of the four identified variants cause severe or moderate loss of CAT-3 function due to altered protein stability or abnormal trafficking to the plasma membrane. The patient with the most deleterious SLC7A3 variant had high-functioning autism and epilepsy, and also carries a de novo 16p11.2 duplication possibly contributing to his phenotype. This study shows that rare hypomorphic variants of SLC7A3 exist in male individuals and suggest that SLC7A3 variants possibly contribute to the etiology of ASD in male subjects in association with other genetic factors. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/25612738 DOI: https://doi.org/10.1159/000369721  Title(2015): Pancreatic response to gold nanoparticles includes decrease of oxidative stress and inflammation in autistic diabetic model.  Gold nanoparticles (AuNPs) have a wide range of applications in various fields. This study provides an understanding of the modulatory effects of AuNPs on an antioxidant system in male Wistar diabetic rats with autism spectrum disorder (ASD). Normal littermates fed by control mothers were injected with citrate buffer alone and served as normal, untreated controls controlin this study. Diabetes mellitus (DM) was induced by administering a single intraperitoneal injection of streptozotocin (STZ) (100 mg/kg) to the pups of (ND) diabetic group, which had been fasted overnight. Autistic pups from mothers that had received a single intraperitoneal injection of 600 mg/kg sodium valproate on day 12.5 after conception were randomly divided into 2 groups (n 2 7/group) as follow; administering single intraperitoneal injection of streptozotocin (STZ) ( (100 mg/kg) to the overnight fasted autistic pups of (AD) autistic diabetic group. The treatment was started on the 5th day after STZ injection with the same dose as in group II and it was considered as 1st day of treatment with gold nanoparticles for 7 days to each rat of (group IV) treated autistic diabetic group(TAD) at a dosage of 2.5 mg/kg. b. wt. At this dose of administration AuNPs, the activities of hepatic superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase were greater in group TAD compared with the control group (P 0.05) in the liver of autistic diabetic AuNPs -supplemented rats, whereas reduced glutathione was markedly higher than in control rats, especially after administration of AuNPs. Moreover, the kidney functions in addition to the fat profile scoring supported the protective potential of that dose of AuNPs. The beta cells revealed euchromatic nuclei with no evidence of separation of nuclear membrane. Our results showed that AuNPs improved many of the oxidative stress parameters (SOD, GPx and, CAT), plasma antioxidant capacity (ORAC) and lipid profile relative to the other parameters. In addition to the apparent reversibility of the pancreatic B cell in group IV which may reflect the regenerative capacity of AuNPs. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/25086736 DOI: https://doi.org/10.1016/j.ridd.2014.07.010  Title(2014): Comparison of urinary oxidative biomarkers in Iranian children with autism.  Autism is a complex neurodevelopmental disorder usually presents in early childhood and thought to be influenced by genetic and environmental factors. Individuals with autism vary widely in abilities, intelligence, and behaviors. It is common for children with autism to exhibit eating disorders and some have preferences for soft and sweetened food making them susceptible to caries. Furthermore, a wide spectrum of medical and behavioral symptoms exhibited by children with autism makes routine dental care very difficult. Intellectual disability is evident in approximately 70% of individuals with autism and most psychiatric disorders, including autism, are associated with increased oxidative stress. 29 subjects diagnosed with autism, in the age group of 6 to 12 years, were a part of the study. Furturemore, 24 normal healthy siblings of same age group were taken as the control group. The present study aimed to evaluate oxidative stress biomarkers such as urinary total antioxidant concentration (TAC), catalase activity (CAT) and total thiol molecules (TTM). The results showed the autism group have significantly higher CAT activity and concomitant lower TAC and TTM concentration in comparison with control group. The results are discussed in relation to an increased vulnerability to oxidative damage, which may contribute to the development and clinical manifestation of symptoms of autism. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/24007566 DOI: https://doi.org/10.1186/2040-2392-4-30  Title(2013): Evidence for differential alternative splicing in blood of young boys with autism spectrum disorders.  Since RNA expression differences have been reported in autism spectrum disorder (ASD) for blood and brain, and differential alternative splicing (DAS) has been reported in ASD brains, we determined if there was DAS in blood mRNA of ASD subjects compared to typically developing (TD) controls, as well as in ASD subgroups related to cerebral volume. RNA from blood was processed on whole genome exon arrays for 2-4-year-old ASD and TD boys. An ANCOVA with age and batch as covariates was used to predict DAS for ALL ASD (n=30), ASD with normal total cerebral volumes (NTCV), and ASD with large total cerebral volumes (LTCV) compared to TD controls (n=20). A total of 53 genes were predicted to have DAS for ALL ASD versus TD, 169 genes for ASD\_NTCV versus TD, 1 gene for ASD\_LTCV versus TD, and 27 genes for ASD\_LTCV versus ASD\_NTCV. These differences were significant at P <0.05 after false discovery rate corrections for multiple comparisons (FDR <5% false positives). A number of the genes predicted to have DAS in ASD are known to regulate DAS (SFPQ, SRPK1, SRSF11, SRSF2IP, FUS, LSM14A). In addition, a number of genes with predicted DAS are involved in pathways implicated in previous ASD studies, such as ROS monocyte/macrophage, Natural Killer Cell, mTOR, and NGF signaling. The only pathways significant after multiple comparison corrections (FDR <0.05) were the Nrf2-mediated reactive oxygen species (ROS) oxidative response (superoxide dismutase 2, catalase, peroxiredoxin 1, PIK3C3, DNAJC17, microsomal glutathione S-transferase 3) and superoxide radical degradation (SOD2, CAT). These data support differences in alternative splicing of mRNA in blood of ASD subjects compared to TD controls that differ related to head size. The findings are preliminary, need to be replicated in independent cohorts, and predicted alternative splicing differences need to be confirmed using direct analytical methods. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/21767826 DOI: https://doi.org/10.1016/j.brainres.2011.06.015  Title(2011): Animal model of autism induced by prenatal exposure to valproate: behavioral changes and liver parameters.  Autism is characterized by behavioral impairments in three main domains: social interaction; language, communication and imaginative play; and range of interests and activities. This syndrome has attracted social attention by its high prevalence. The animal model induced by prenatal exposure to valproic acid (VPA) has been proposed to study autism. Several characteristics of behavioral abnormalities found in the VPA rats, such as repetitive/stereotypic-like activity and deficit in social interaction have been correlated with autism. Features like flexibility to change strategy, social memory and metabolic status of the induced rats have not been examined. Thus, the main aim of this work was to investigate additional behavioral rodent similarities with autism, as well as, liver redox parameters after prenatal exposure to VPA. Young rats from the VPA group presented aberrant approach to a stranger rat, decreased conditioned place preference to conspecifics, normal spatial learning and a lack of flexibility to change their strategy. As adults, they presented inappropriate social approach to a stranger rat, decreased preference for social novelty, apparently normal social recognition and no spatial learning deficits. Examination of the liver from the VPA group presented significantly increased (12%) levels of catalase (CAT) activity, no alteration in superoxide dismutase (SOD) activity and a decrease in the SOD/CAT ratio. TBARS, sulfhydril and carbonyl contents, and serum levels of aminotransferases remained unchanged. In summary, rats prenatally exposed to VPA presented decreased flexibility to change strategy and social impairments similar to the autism symptoms, contributing to the understanding of neurodevelopmental symptoms and oxidative imbalance associated to the autism spectrum disorder. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/21236316 DOI: https://doi.org/10.1016/j.neulet.2011.01.019  Title(2011): A functional tetranucleotide (AAAT) polymorphism in an Alu element in the NF1 gene is associated with mental retardation.  Mental retardation (MR) is frequent in neurofibromatosis type 1 (NF1). Allele 5 of a tetranucleotide polymorphism in an Alu element (GXAlu) localized in intron 27b of the NF1 gene has previously been associated with autism. We considered that the microsatellite GXAlu could also represent a risk factor in MR without autism. We developed a rapid method for genotyping by non-denaturing HPLC and assayed the allelic variation of GXAlu marker on in vitro gene expression in Cos-7 cells. A French population of 157 individuals (68 non syndromic non familial MR (NS-MR) patients diagnosed in the University Hospital of Tours; 89 controls) was tested in a case-control assay. We observed a significant association (χ(2)=7.96; p=0.005) between alu4 carriers (7 AAAT repeats) and MR (OR: 7.86; 95% C.I.: 2.13-28.9). The relative in vitro expression of a reporter gene encoding chloramphenicol acetyl transferase (CAT) was higher for alu4 and alu5, suggesting a regulation effect for these alleles on gene expression in vivo. Our results showed an association with a polymorphism regulating the NF1 gene or other genes during brain development. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/15205966 DOI: https://doi.org/10.1007/s00406-004-0456-7  Title(2004): Increased oxidative stress and altered activities of erythrocyte free radical scavenging enzymes in autism.  There is great evidence in recent years that oxygen free radicals play an important role in the pathophysiology of many neuropsychiatric disorders. The present study was performed to assess the changes in red blood cells thiobarbituric acid-reactive substances (TBARS) levels, and superoxide dismutase (SOD), catalase (CAT), adenosine deaminase (ADA) and xanthine oxidase (XO) activities in patients with autism (n = 27) compared to age- and sex-matched normal controls (n = 26). In the autistic group, increased TBARS levels (p < 0.001) and XO (p < 0.001) and SOD (p < 0.001) activity, decreased CAT (p < 0.001) activity and unchanged ADA activity were detected. It is proposed that antioxidant status may be changed in autism and this new situation may induce lipid peroxidation. These findings indicated a possible role of increased oxidative stress and altered enzymatic antioxidants, both of which may be relevant to the pathophysiology of autism. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/37110206 DOI: https://doi.org/10.3390/metabo13040548  Title(2023): Bee Pollen and Probiotics' Potential to Protect and Treat Intestinal Permeability in Propionic Acid-Induced Rodent Model of Autism.  Rodent models may help investigations on the possible link between autism spectrum disorder (ASD) and gut microbiota since autistic patients frequently manifested gastrointestinal troubles as co-morbidities. Thirty young male rats were divided into five groups: Group 1 serves as control; Group 2, bee pollen and probiotic-treated; and Group 3, propionic acid (PPA)-induced rodent model of autism; Group 4 and Group 5, the protective and therapeutic groups were given bee pollen and probiotic combination treatment either before or after the neurotoxic dose of PPA, respectively. Serum occludin, zonulin, lipid peroxides (MDA), glutathione (GSH), glutathione-S-transferase (GST), glutathione peroxidase (GPX), catalase, and gut microbial composition were assessed in all investigated groups. Recorded data clearly indicated the marked elevation in serum occludin (1.23 ± 0.15 ng/mL) and zonulin (1.91 ± 0.13 ng/mL) levels as potent biomarkers of leaky gut in the PPA- treated rats while both were normalized to bee pollen/probiotic-treated rats. Similarly, the high significant decrease in catalase (3.55 ± 0.34 U/dL), GSH (39.68 ± 3.72 µg/mL), GST (29.85 ± 2.18 U/mL), and GPX (13.39 ± 1.54 U/mL) concomitant with a highly significant increase in MDA (3.41 ± 0.12 µmoles/mL) as a marker of oxidative stress was also observed in PPA-treated animals. Interestingly, combined bee pollen/probiotic treatments demonstrated remarkable amelioration of the five studied oxidative stress variables as well as the fecal microbial composition. Overall, our findings demonstrated a new approach to the beneficial use of bee pollen and probiotic combination as a therapeutic intervention strategy to relieve neurotoxic effects of PPA, a short-chain fatty acid linked to the pathoetiology of autism. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/37078811 DOI: https://doi.org/10.55782/ane-2023-003  Title(2023): Effects of varied‑intensity endurance exercise training on oxidative and antioxidant factors in the liver of rats with valproic acid‑induced autism.  Autism spectrum disorders are complex behavioral disorders that can be caused by exposure to valproic acid (VPA) during pregnancy. A therapeutic role for exercise training has been reported in many neurological diseases and problems, including autism. We aimed to evaluate various intensities of endurance exercise training and investigate its effects on oxidative and antioxidant factors in the liver of young males in a rat model of autism. Female rats were divided into a treatment (autism) and a control group. The autism group received VPA intraperitoneally on day 12.5 of pregnancy and the control pregnant females received saline. On the 30th day post‑birth, a social interaction test was performed on the offspring to confirm autistic‑like behavior. Offspring were divided into three subgroups: no exercise, mild exercise training, and moderate exercise training. Then the oxidative index of malondialdehyde (MDA) and the antioxidant indices of superoxide dismutase (SOD), total antioxidant capacity (TAC), and catalase in liver tissue were examined. The results of this study showed that both indices of sociability and social novelty decreased in the autism group. MDA levels in the liver of the autistic group increased, and moderate exercise training was shown to reduce the levels. Catalase and SOD activity as well as TAC levels decreased in the autism group, and moderate‑intensity exercise training was shown to increase the values. Parameters of hepatic oxidative stress were altered in VPA‑induced autism, and moderate‑intensity endurance exercise training was demonstrated to have beneficial effects on hepatic oxidative stress factors by modul ating the antioxidant/oxidant ratio. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/36837929 DOI: https://doi.org/10.3390/metabo13020310  Title(2023): Prenatal SSRI Exposure Increases the Risk of Autism in Rodents via Aggravated Oxidative Stress and Neurochemical Changes in the Brain.  The mechanisms underlying selective serotonin reuptake inhibitor (SSRI) use during pregnancy as a major autism risk factor are unclear. Here, brain neurochemical changes following fluoxetine exposure and in an autism model were compared to determine the effects on autism risk. The study was performed on neonatal male western albino rats which were divided into Groups one (control), two (propionic acid [PPA]-induced autism model), and three (prenatal SSRI-exposed newborn rats whose mothers were exposed to 5 mg/kg of fluoxetine over gestation days 10-20). SSRI (fluoxetine) induced significant neurochemical abnormalities in the rat brain by increasing lipid peroxide (MDA), Interferon-gamma (IFN-γ), and caspase-3 levels and by depleting Glutathione (GSH), Glutathione S-transferases (GST), Catalase, potassium (K+), and Creatine kinase (CK) levels, similarly to what has been discovered in the PPA model of autism when compared with control. Prenatal fluoxetine exposure plays a significant role in asset brain damage in newborns; further investigation of fluoxetine as an autism risk factor is thus warranted. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/36113682 DOI: https://doi.org/10.1016/j.brainresbull.2022.09.003  Title(2022): Homotaurine ameliorates the core ASD symptomatology in VPA rats through GABAergic signaling: Role of GAD67.  Dysregulated GABAergic signaling is reported in Autism Spectrum disorder (ASD). In the present study, we evaluated a GABA structural mimicker homotaurine (HT) via in-silico docking and investigated the therapeutic efficacy of this drug to ameliorate ASD symptoms in the valproic acid (VPA) rat model of ASD. For the in-vivo study, animals were divided into two groups [Normal control (NC, 0.9 % saline; i.p) and disease control (VPA 600 mg/kg; i.p)] on gestational day (GD) 12.5. Male pups from VPA-exposed mothers were further divided into five groups (n = 6 in each group): disease control (DC, no-further treatment), standard treatment (risperidone (RES) 2.5 mg/kg; i.p, consecutively from PND 23-43), HT (10, 25 and 50 mg/kg; i.p, consecutively from PND 23-43). In in-silico studies, the binding pattern of homotaurine to GABA-A receptor was found similar to GABA with Tyr205, Glu155, Tyr157, Arg6, and Thr 130 as shared residues. In the in-vivo phase, the early developmental parameters (from PND 7-23) and behavioral parameters (from PND 43-54) were assessed. The offsprings of the VPA exposed group exhibited significant (p < 0.05) developmental delays, behavioral deficits [decreased sociability and social novelty (three-chamber sociability test), spatial memory (Morris water maze), increased stereotypy (self-grooming)], increased oxidative stress (decreased GSH, SOD, Catalase, and increased MDA), increased pro-inflammatory (IL-1β, 6, TNF-α) and decreased anti-inflammatory (IL-10) cytokines, Purkinje cell loss in the cerebellum and pyknosis in PFC (H/E, Nissil staining) and decreased GAD67 expression in the cerebellum (RT-PCR & immunohistochemistry). Compared to the DC, HT treatment (50 mg/kg) was able to ameliorate the aberrant core behavioral deficits, decreased oxidative stress, decreased pro-inflammatory and increased anti-inflammatory cytokine profile with preservation of the Purkinje cell density in the cerebellum, decreased pyknosis in the prefrontal cortex and normalized the expression of GAD67. Thus, HT can be a useful therapeutic agent in ASD and requires further clinical evaluation. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/35883877 DOI: https://doi.org/10.3390/antiox11071386  Title(2022): Oxidative Stress and Psychiatric Disorders: Evidence from the Bidirectional Mendelian Randomization Study.  Observational studies have shown that oxidative stress is highly related to psychiatric disorders, while its cause−effect remains unclear. To this end, a Mendelian randomization study was performed to investigate the causal relationship between oxidative stress and psychiatric disorders. On the one hand, all causal effects of oxidative stress injury biomarkers (OSIB) on psychiatric disorders were not significant (p > 0.0006), while the findings suggested that part of OSIB was nominally associated with the risk of psychiatric disorders (causal OR of uric acid (UA), 0.999 for bipolar disorder (BD), and 1.002 for attention-deficit/hyperactivity disorder (ADHD); OR of catalase was 0.903 for anorexia nervosa (AN); OR of albumin was 1.162 for autism; p < 0.05). On the other hand, major depressive disorder (MDD) was significantly associated with decreased bilirubin (p = 2.67 × 10−4); ADHD was significantly associated with decreased ascorbate (p = 4.37 × 10−5). Furthermore, there were also some suggestively causal effects of psychiatric disorders on OSIB (BD on decreased UA and increased retinol; MDD on increased UA and decreased ascorbate; schizophrenia on decreased UA, increased retinol and albumin; ADHD on increased UA, and decreased catalase, albumin, and bilirubin; AN on decreased UA). This work presented evidence of potential causal relationships between oxidative stress and psychiatric disorders. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/35346813 DOI: https://doi.org/10.1016/j.jep.2022.115199  Title(2022): Neuroprotective effect of the standardised extract of Bacopa monnieri (BacoMind) in valproic acid model of autism spectrum disorder in rats.  Bacopa monnieri (BM) is commonly employed in the Indian traditional system of medicines, i.e. Ayurveda as a memory booster, antioxidant, anti-inflammatory, antipyretic, analgesic, sedative and anti-epileptic for decades. To evaluate the neuroprotective effect of Bacopa monnieri (BM) in experimental model of autism spectrum disorder (ASD) in Wistar rats and explore its mechanism of action. BacoMind, was evaluated for its neuroprotective effect in valproic acid (VPA) model of ASD. For in-vivo study, the pregnant female Wistar rats were divided in two groups; normal control (NC) and VPA group who received single dose of normal saline (0.9%) or 600 mg/kg dose of VPA respectively on gestation day (G.D) 12.5. After the birth, all pups were segregated according to the sex. All the male pups from the dams were divided into six groups: Group 1 (NC, treated with only 0.9% normal saline, group 2 (VPA, treated 600 mg/kg on G.D12.5 and normal saline from post natal day (PND) 23 to 43), group 3 (risperidone 2.5 mg/kg, PND 23 to 43) and groups 4, 5 and 6 (BM 20, 40, 80 mg/kg, PND 23 to 43). All experimental groups were subjected to batteries of behavior parameters (three chamber sociability test, Morris Water Maze, elevated plus maze, open field and rota rod test), biochemical parameters such as oxidative stress (GSH, SOD, Catalase, MDA), inflammatory cytokines (Il-1β, IL-6, IL-10, TNF-α), histopathological examination (cresyl violet staining) of hippocampus (HC) and prefrontal cortex (PFC) regions. Further, the mRNA as well as protein expression of AMPA receptor was evaluated using RT-PCR and western blot respectively to study the mechanism of neuroprotective effect of BM. The in-silico analysis followed evaluating the binding profile of different constituents of BacoMind with AMPA receptor. The results of the in-vivo study indicated BM at 80 mg/kg ameliorated abnormal behavioral paradigms such as social deficits, repetitive behavior, learning and memory impairments, and motor coordination exhibited by the VPA model of ASD in rats. Furthermore, BM was found to have a significant anti-oxidant (increasing GSH, SOD, and catalase and decreasing MDA levels) and anti-inflammatory properties (decreasing IL-1β, 6, TNF- α). The histopathological score was also found to be significantly improved by BM in a dose dependent manner in both HC and PFC. In addition to this, the up-regulated mRNA as well as protein expression of AMPA receptor was significantly reduced by 80 mg/kg dose of BM in both HC and PFC. Further, the in-silico analysis of different constituents of BacoMind with AMPA receptor demonstrated that luteolin and apigenin showed good binding to both the competitive antagonist binding site, non-competitive antagonist binding site and allosteric modulator site while Bacosaponin C showed good binding to the non-competitive antagonist binding site. The present study concluded that BM can be a potential candidate for ameliorating the ASD symptoms in rats and acts via modulating the up-regulated AMPA receptor expression. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/34984596 DOI: https://doi.org/10.1007/s12011-021-03083-5  Title(2022): Centella asiatica Alleviates AlCl3-induced Cognitive Impairment, Oxidative Stress, and Neurodegeneration by Modulating Cholinergic Activity and Oxidative Burden in Rat Brain.  Aluminum (Al) is linked to the development of many neurological disorders such as Alzheimer's disease (AD), Parkinson's disease, and autism. Centella asiatica (CA) is a regenerating herb traditionally used to stimulate memory. This study was designed to assess the neuroprotective role of ethanolic extract of CA (CAE) in AlCl3-induced neurological conditions in rats. Adult rats were chronically treated with AlCl3 (100 mg/kg b.w./day) for 60 days to establish the dementia model, and co-administration of CAE was evaluated for its ability to attenuate the toxic effect of AlCl3. CAE was given orally at a dose of 150 and 300 mg/kg b.w./day, for 60 days. The behavioral performances of rats were tested through Y-maze and open field tests. Lipid peroxidation, superoxide dismutase, and catalase activity were evaluated to measure oxidative stress; and acetylcholinesterase (AChE) activity was assessed to evaluate cholinergic dysfunction in the rat brain. H&E staining was used to assess structural abnormalities in the cortex and hippocampus. The result showed that AlCl3 induces cognitive dysfunction (impaired learning and memory, anxiety, diminished locomotor activity), oxidative stress, cholinergic impairment, and histopathological alteration in the rat brain. Co-administration of CAE with AlCl3 markedly protects the brain from AlCl3-induced cognitive dysfunction, oxidative stress, AChE activity, and cytoarchitectural alterations. Furthermore, 15 days CAE treatment after 45 days AlCl3 administration markedly ameliorates the AlCl3-induced neurotoxicity indicating its potential for therapeutic use. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/34528217 DOI: https://doi.org/10.1007/s12035-021-02546-z  Title(2021): Lead (Pb)-induced oxidative stress mediates sex-specific autistic-like behaviour in Drosophila melanogaster.  Autism spectrum disorder (ASD) is a highly prevalent neurodevelopmental disorder characterised by three main behavioural symptoms: abnormal social interaction, verbal and non-verbal communication impairments, and repetitive and restricted activities or interests. Even though the exact aetiology of ASD remains unknown, studies have shown a link between genetics and environmental pollutants. Heavy metal lead (Pb), the environmental pollutant, is associated with ASD. Pb may also exhibit sex-specific ASD behaviour, as has been demonstrated in the global human populations. Drosophila melanogaster as a model has been used in the present study to understand the involvement of Pb-induced oxidative stress in developing ASD behaviour. The larval feeding technique has been employed to administer different Pb concentrations (0.2-0.8 mM) to Oregon-R (ORR), superoxide dismutase (Sod), or catalase (Cat) antioxidants overexpressed or knockdown flies. Adult Drosophila (5-day old) were used for Pb content, biochemical, and behavioural analysis.Pb accumulated in the Drosophila brain induces oxidative stress and exhibited a human autistic-like behaviour such as reduced climbing, increased grooming, increased social spacing, and decreased learning and memory in a sex-specific manner.Pb-induced autistic-like behaviour was intensified in Sod or Cat-knockdown flies, whereas Sod or Cat-overexpressed flies overcome that behavioural alterations. These results unequivocally proved that Pb-induced oxidative stress causes ASD behaviour of humans in Drosophila. Thus, Drosophila is used as a model organism to analyse ASD-like human behaviour and underlines the importance of using antioxidant therapy in alleviating ASD symptoms in children. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/33913688 DOI: https://doi.org/10.1021/acschemneuro.0c00672  Title(2021): Inhibition of the ERK1/2 Phosphorylation by Dextromethorphan Protects against Core Autistic Symptoms in VPA Induced Autistic Rats: In Silico and in Vivo Drug Repurposition Study.  The imbalance between excitatory and inhibitory neurotransmitters is explicitly related to the pathophysiology of autism spectrum disorder (ASD). The role of an NMDA receptor antagonist, dextromethorphan, was studied in ameliorating the ASD-like symptoms by regulating the excitatory and inhibitory imbalance using the valproic acid (VPA) model of ASD. Female Wistar rats were administered VPA [600 mg/kg on embryonic day ED-12.5] through intraperitoneal (ip) injection to induce ASD in pups. Autistic pups were then given dextromethorphan (10, 15, and 30 mg/kg; ip) and risperidone (2.5 mg/kg; ip) from PND 23 to 43 in different groups. Behavioral tests (three chamber sociability, self-grooming, Morris water maze, elevated plus maze, open field, rotarod, grip strength), oxidative stress and inflammatory markers, histological evaluation (H&E, Nissil staining), and NMDA and ERK1/2 expression by immunohistochemistry and RT-PCR were done. The in silico modeling of dextromethorphan against PPDA, TCN-201, MK-22, EVT-101 on NMDA receptors was also performed. Dextromethorphan (30 mg/kg) rescued the impaired behavioral patterns including social excitability, hyperactivity, repetitive and restricted behaviors as well as mitigation of the memory and motor coordination. The levels of various oxidative stress markers (GSH, SOD, catalase, MDA) and inflammatory markers (IL-1β, IL-6, IL-10, TNF-α) were ameliorated by different doses of dextromethorphan. It also reduced the neuronal injury score and rescued the overly expressed pERK1/2 and NMDA signaling in both the prefrontal cortex and hippocampus of the autistic pups. In silico results showed favorable binding of dextromethorphan against TCN-201 and MK-22 binding sites. The present study provided experimental evidence for the potential therapeutic role of dextromethorphan in attenuating autism symptomatology in the ASD model of rats. Thus, modulation of the glutamatergic signaling can be a potential target for ASD treatment. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/33785420 DOI: https://doi.org/10.1016/j.neuint.2021.105036  Title(2021): Astrocyte-mediated disruption of ROS homeostasis in Fragile X mouse model.  Astrocytes, glial cells within the brain, work to protect neurons during high levels of activity by maintaining oxidative homeostasis via regulation of energy supply and antioxidant systems. In recent years, mitochondrial dysfunction has been highlighted as an underlying factor of pathology in many neurological disorders. In animal studies of Fragile X Syndrome (FXS), the leading genetic cause of autism, higher levels of reactive oxygen species, lipid peroxidation, and protein oxidation within the brain indicates that mitochondria function is also altered in FXS. Despite their integral contribution to redox homeostasis within the CNS, the role of astrocytes on the occurrence or progression of neurodevelopmental disorders in this way is rarely considered. This study specifically examines changes to astrocyte mitochondrial function and antioxidant expression that may occur in FXS. Using the Fmr1 knockout (KO) mouse model, mitochondrial respiration and reactive oxygen species (ROS) emission were analyzed in primary cortical astrocytes. While mitochondrial respiration was similar between genotypes, ROS emission was significantly elevated in Fmr1 KO astrocytes. Notably, NADPH-oxidase 2 expression in Fmr1 KO astrocytes was also enhanced but only changes in catalase antioxidant enzyme expression were noted. Characterization of astrocyte factors involved in redox imbalance is invaluable to uncovering potential sources of oxidative stress in neurodevelopmental disorders and more specifically, the intercellular mechanisms that contribute to dysfunction in FXS. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/33669336 DOI: https://doi.org/10.3390/ijms22041947  Title(2021): The Multi-Targeting Ligand ST-2223 with Histamine H3 Receptor and Dopamine D2/D3 Receptor Antagonist Properties Mitigates Autism-Like Repetitive Behaviors and Brain Oxidative Stress in Mice.  Autism spectrum disorder (ASD) is a complex heterogeneous neurodevelopmental disorder characterized by social and communicative impairments, as well as repetitive and restricted behaviors (RRBs). With the limited effectiveness of current pharmacotherapies in treating repetitive behaviors, the present study determined the effects of acute systemic treatment of the novel multi-targeting ligand ST-2223, with incorporated histamine H3 receptor (H3R) and dopamine D2/D3 receptor affinity properties, on ASD-related RRBs in a male Black and Tan BRachyury (BTBR) mouse model of ASD. ST-2223 (2.5, 5, and 10 mg/kg, i.p.) significantly mitigated the increase in marble burying and self-grooming, and improved reduced spontaneous alternation in BTBR mice (all p p p p < 0.05). These preliminary in vivo findings demonstrate the ameliorative effects of ST-2223 on RRBs in a mouse model of ASD, suggesting its pharmacological prospective to rescue core ASD-related behaviors. Further confirmatory investigations on its effects on various brain neurotransmitters, e.g., dopamine and histamine, in different brain regions are still warranted to corroborate and expand these initial data. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/33220538 DOI: https://doi.org/10.1016/j.envint.2020.106253  Title(2021): Glyphosate targets fish monoaminergic systems leading to oxidative stress and anxiety.  Glyphosate is the active ingredient of some of the most highly produced and used herbicides worldwide. The intensive applications of glyphosate-based herbicides and its half-life in water lead to its presence in many aquatic ecosystems. Whereas recent studies have reported neurotoxic effects of glyphosate including autism-related effects, most of them used extremely high (mg/L to g/L) concentrations, so it is still unclear if chronic, low environmentally relevant concentrations of this compound (ng/L to μg/L) can induce neurotoxicity. In this study we analyzed the neurotoxicity of glyphosate in adult zebrafish after waterborne exposure to environmentally relevant concentrations (0.3 and 3 μg/L) for two weeks. Our data showed that exposed fish presented a significant impairment of exploratory and social behaviors consistent with increased anxiety. The anterior brain of the exposed fish presented a significant increase in dopamine and serotonin levels, as well as in the DOPAC/dopamine and homovanillic acid/dopamine turnover ratios. Moreover, the expression of genes involved in the dopaminergic system, as th1, th2, comtb, and scl6a3 was downregulated. Finally, the brain of exposed fish presented a significant increase in the catalase and superoxide dismutase activities, with a concomitant decrease of glutathione stores. These changes in the antioxidant defense system are consistent with the observed increase in oxidative stress, reflected by the increase in the levels of lipid peroxidation in the brain. The presented results show that current glyphosate concentrations commonly found in many aquatic ecosystems may have detrimental consequences on fish survival by decreasing exploration of the environment or altering social interactions. Furthermore, as zebrafish is also a vertebrate model widely used in human neurobehavioral studies, these results are relevant not only for environmental risk assessment, but also for understanding the risk of chronic low-dose exposures on human health. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/32876824 DOI: https://doi.org/10.1007/s11011-020-00610-6  Title(2020): Exposure to a high dose of amoxicillin causes behavioral changes and oxidative stress in young zebrafish.  Autistic spectrum disorder (ASD) is a group of early-onset neurodevelopmental disorders characterized by impaired social and communication skills. Autism is widely described as a behavioral syndrome with multiple etiologies where may exhibit neurobiological, genetic, and psychological deficits. Studies have indicated that long term use of antibiotics can alter the intestinal flora followed by neuroendocrine changes, leading to behavioral changes. Indeed, previous studies demonstrate that a high dose of amoxicillin can change behavioral parameters in murine animal models. The objective was to evaluate behavioral and oxidative stress parameters in zebrafish exposed to a high dose of amoxicillin for 7 days. Young zebrafish were exposed to a daily concentration of amoxicillin (100 mg/L) for 7 days. Subsequently, the behavioral analysis was performed, and the brain content was dissected for the evaluation of oxidative stress parameters. Zebrafish exposed to a high dose of amoxicillin showed locomotor alteration and decreased social interaction behavior. In addition, besides the significant decrease of sulfhydryl content, there was a marked decrease in catalase activity, as well as an increased superoxide dismutase activity in brain tissue. Thus, through the zebrafish model was possible to note a central effect related to the exposition of amoxicillin, the same as observed in murine models. Further, the present data reinforce the relation of the gut-brain-axis and the use of zebrafish as a useful tool to investigate new therapies for autistic traits. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/32503208 DOI: https://doi.org/10.3390/ijms21113996  Title(2020): The Dual-Active Histamine H3 Receptor Antagonist and Acetylcholine Esterase Inhibitor E100 Alleviates Autistic-Like Behaviors and Oxidative Stress in Valproic Acid Induced Autism in Mice.  The histamine H3 receptor (H3R) functions as auto- and hetero-receptors, regulating the release of brain histamine (HA) and acetylcholine (ACh), respectively. The enzyme acetylcholine esterase (AChE) is involved in the metabolism of brain ACh. Both brain HA and ACh are implicated in several cognitive disorders like Alzheimer's disease, schizophrenia, anxiety, and narcolepsy, all of which are comorbid with autistic spectrum disorder (ASD). Therefore, the novel dual-active ligand E100 with high H3R antagonist affinity (hH3R: Ki = 203 nM) and balanced AChE inhibitory effect (EeAChE: IC50 = 2 µM and EqBuChE: IC50 = 2 µM) was investigated on autistic-like sociability, repetitive/compulsive behaviour, anxiety, and oxidative stress in male C57BL/6 mice model of ASD induced by prenatal exposure to valproic acid (VPA, 500 mg/kg, intraperitoneal (i.p.)). Subchronic systemic administration with E100 (5, 10, and 15 mg/kg, i.p.) significantly and dose-dependently attenuated sociability deficits of autistic (VPA) mice in three-chamber behaviour (TCB) test (all p p p p p < 0.05). These results demonstrate the promising effects of E100 on in-vivo VPA-induced ASD-like features in mice, and provide evidence that a potent dual-active H3R antagonist and AChE inhibitor (AChEI) is a potential drug candidate for future therapeutic management of autistic-like behaviours. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/32006361 DOI: https://doi.org/10.1007/978-3-030-30402-7\_7  Title(2020): Role of Oxidative Stress and Antioxidants in Autism.  Autism spectrum disorder (ASD) is a heterogeneous group of neurodevelopmental disorders with poorly understood etiology that are defined exclusively on the basis of behavioral observations. This disorder has been linked to increased levels of oxidative stress and lower antioxidant capacity. Oxidative stress in autism has been studied at the membrane level and also by measuring products of lipid peroxidation, detoxifying agents (such as glutathione), and antioxidants involved in the defense system against reactive oxygen species (ROS). Several studies have suggested alterations in the activities of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase in autism. Additionally, altered glutathione levels and homocysteine/methionine metabolism, increased inflammation, excitotoxicity, as well as mitochondrial and immune dysfunction have been suggested in autism. Moreover, environmental and genetic risk factors may intensify vulnerability to oxidative stress in autism. Collectively, these studies suggest increased oxidative stress in autism that may contribute to the development of this disease both in terms of pathogenesis and clinical symptoms. Antioxidant supplementation, or ways to improve the altered metabolite levels in the interconnected transmethylation and transsulfuration pathways, has been associated with decreased autistic behaviors and severity. This chapter provides a conceptual framework on oxidative stress and antioxidants utility. These types of interventions should be further studied in order to determine their effectiveness at improving metabolic imbalances. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/31226268 DOI: https://doi.org/10.1016/j.neuro.2019.06.004  Title(2019): Maternal glyphosate-based herbicide exposure alters antioxidant-related genes in the brain and serum metabolites of male rat offspring.  In response to the rapid development of genetically engineered glyphosate-tolerant crops, the use of glyphosate-based herbicides (GBHs), in agriculture, has increased substantially. Currently, it is estimated that 747 million kg of GBHs are applied per year. Although several epidemiological studies have demonstrated that there are health risks associated with GBH exposure, the effects these chemicals have on the oxidative and inflammatory response in the brain are still unclear. In fact, alterations in these processes could contribute to the development of neurological diseases, such as Alzheimer's disease and autism spectrum disorders. The present study exposed pregnant rats to GBH and evaluated changes in the expression of genes related to oxidnte defense and inflammation response and monitored the serum metabolome in the adult male offspring. Pregnant Wistar rats were administered distilled water or Roundup®, at either 5 and 50 mg/kg/day, (p.o.) from gestational day (GD) 18 to postnatal day (PND) 5. There was a significant increase in the gene expression levels of Neuroglobin (Ngb - oxygen storage and tissue protection) (105%, p = 0.031), Glutathione Peroxidase 1 (Gpx1 - oxidative stress) (95%, p = 0.005), Prostaglandin-Endoperoxidase Synthase 1 (Ptgs1 - inflammation) (109%, p = 0.033) and Hypoxia inducible factor 1 subunit alpha (Hif1α - oxygen sensor) (73%, p = 0.017), in the cerebellum of PND90 rats perinatally exposed to 50 mg GBH/kg/day. Moreover, both GBH-exposed groups displayed a significant decrease in the expression of Catalase (Cat - oxidative stress) (49%, p = 0.003; and 31% p = 0.050, respectively) expression, in the cortex. Serum metabolites analyses, from the same animals of each group, demonstrated that there were significant changes in the concentrations of lysophosphatidylcholine and phosphatidylcholine, which have been associated with neurodegenerative diseases. The results of the present study suggest GBH exposure during pregnancy alters the expression of genes associated with oxidant defense, inflammation and lipid metabolism. It is plausible that maternal GBH exposure could have lasting neuronal effects on the offspring later in life. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/30784006 DOI: https://doi.org/10.1007/s12017-019-08526-w  Title(2019): Optogenetic Stimulation of the Anterior Cingulate Cortex Ameliorates Autistic-Like Behaviors in Rats Induced by Neonatal Isolation, Caudate Putamen as a Site for Alteration.  Epigenetic agents, such as neonatal isolation during neurodevelopmental period of life, can change various regions of the brain. It may further induce psychological disorders such as autistic-like phenomena. This study indicated the role of chronic increased anterior cingulate cortex (ACC) output on alteration of caudate putamen (CPu) as a main behavior regulator region of the brain in adult maternal deprived (MD) rats. For making an animal model, neonates were isolated from their mothers in postnatal days (PND 1-10, 3 h/day). Subsequently, they bilaterally received pLenti-CaMKIIa-hChR2 (H134R)-mCherry-WPRE virus in ACC area via stereotaxic surgery in PND50. After 22 days, these regions were exposed to blue laser (473 nm) for six consecutive days (15 min/day). Then, behavioral deficits were tested and were compared with control group in the following day. Animals were immediately killed and their brains were prepared for tissue processing. Results showed that neonatal isolation induces autistic-like behaviors and leads to overexpression of NMDAR1 and Nox2-gp91phox proteins and elevation of catalase activity in the CPu regions of the adult offspring compared with control group. Chronic optogenetic stimulation of ACC neurons containing (ChR2+) led to significant reduction in the appearance of stereotypical behavior and alien-phobia in MD rats. The amount of NMDAR1 and Nox2-gp91phox expression and the catalase activity in CPu were reduced after this treatment. Therefore, autistic-like behavior seems to be related with elevation of NMDAR1 and Nox2-gp91phox protein levels that enhance the effect of glutamatergic projection on CPu regions. Optogenetic treatment also could ameliorate behavioral deficits by modulating these protein densities. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/28497358 DOI: https://doi.org/10.1007/s11011-017-0029-x  Title(2017): Predictive value of selected biomarkers related to metabolism and oxidative stress in children with autism spectrum disorder.  Autism spectrum disorder (ASD) as a neurodevelopmental disorder is characterized by impairments in social interaction, communication, and restricted, repetitive behavior. Several and reproducible studies have suggested that oxidative stress may represent one of the primary etiological mechanism of ASD that can be targeted for therapeutic intervention. In the present study, multiple regression and combined receiver operating characteristic (ROC) analysis were used to search for a relationship between impaired energy and oxidative metabolic pathways in the etiology of ASD and to find the linear combination that maximizes the partial area under a ROC curve for a pre-identified set of markers related to energy metabolism and oxidative stress. Thirty children with ASD and 30 age and gender matched controls were enrolled in the study. Using either spectrophotometric or ELISA-colorimetric assay, levels of lipid peroxides, vitamin E, vitamin C, glutathione (GSH)/glutathione disulfide (GSSG) together with the enzymatic activity of catalase, plasma glutathione peroxidase (GPx), and blood superoxide dismutase (SOD), were measured in peripheral blood samples, as biomarkers related to oxidative stress. Creatine kinase, ectonucleotidases (ADPase and ATPase) Na+/K+ (ATPase), lactate, inorganic phosphate, and levels of adenosine monophosphate (AMP), adenosine diphosphate (ADP), and adenosine triphosphate (ATP) together with adenylate energy charge, were also measured as markers of impaired energy metabolism. Statistical analysis using ROC curves, multiple and logistic regression were performed. A remarkable increase in the area under the curve for most of the combined markers, representing both energy impaired metabolism or oxidative stress, was observed by using combined ROC analyses. Moreover, higher specificity and sensitivity of the combined markers were also reported. The present study indicated that the measurement of the predictive value of selected biomarkers related to energy metabolism and oxidative stress in children with ASD using ROC analysis should lead to the better identification of the etiological mechanism of ASD associated with metabolism and diet. Agents with activity against the impaired metabolic pathway associated with ASD including the metabolic defects and involved enzymes hold a promise as a novel therapy for ASD. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/27034117 DOI: https://doi.org/10.1016/j.brainresbull.2016.03.013  Title(2016): Memantine ameliorates autistic behavior, biochemistry & blood brain barrier impairments in rats.  Autism spectrum disorder (ASD) is a neurodevelopmental disorder, commonly characterized by altered social behavior, communication, biochemistry and pathological conditions. One percent of the worldwide population suffers from autism and males suffer more than females. NMDA receptors have the important role in neurodevelopment, neuropsychiatric and neurodegenerative disorders. This study has been designed to investigate the role of memantine, a NMDA receptor modulator, in prenatal valproic acid-induced autism in rats. Animals with prenatal valproic acid have shown the reduction in social interaction (three-chamber social behavior apparatus), spontaneous alternation (Y-Maze), exploratory activity (Hole board test), intestinal motility, serotonin levels (both in prefrontal cortex and ileum) and prefrontal cortex mitochondrial complex activity (complex I, II, IV). Furthermore, prenatal valproic acid-treated animals have shown an increase in locomotion (actophotometer), anxiety (elevated plus maze), brain oxidative stress (thiobarbituric acid reactive species, glutathione, catalase), nitrosative stress (nitrite/nitrate), inflammation (both in brain and ileum myeloperoxidase activity), calcium and blood-brain barrier permeability. Treatment with memantine has significantly attenuated prenatal valproic acid-induced reduction in social interaction, spontaneous alteration, exploratory activity intestinal motility, serotonin levels and prefrontal cortex mitochondrial complex activity. Furthermore, memantine has also attenuated the prenatal valproic acid-induced increase in locomotion, anxiety, brain oxidative and nitrosative stress, inflammation, calcium and blood-brain barrier permeability. Thus, it may be concluded that prenatal valproic acid has induced autistic behavior, biochemistry and blood-brain barrier impairment in animals, which were significantly attenuated by memantine. NMDA receptor modulators like memantine should be explored further for the therapeutic benefits in autism. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/26551768 DOI: https://doi.org/10.1016/j.brainres.2015.10.052  Title(2016): Minocycline ameliorates prenatal valproic acid induced autistic behaviour, biochemistry and blood brain barrier impairments in rats.  Autism is a neurodevelopment disorder. One percent worldwide population suffers with autism and males suffer more than females. Microglia plays an important role in neurodevelopment, neuropsychiatric and neurodegenerative disorders. The present study has been designed to investigate the role of minocycline in prenatal valproic acid induced autism in rats. Animals with prenatal valproic acid have reduced social interaction (three chamber social behaviour apparatus), spontaneous alteration (Y-Maze), exploratory activity (Hole board test), intestinal motility, serotonin levels (both in prefrontal cortex and ileum) and prefrontal cortex mitochondrial complex activity (complexes I, II, IV). Furthermore, prenatal valproic acid treated animals have shown an increase in locomotion (actophotometer), anxiety (elevated plus maze), brain oxidative stress (thiobarbituric acid reactive species, glutathione, catalase), nitrosative stress (nitrite/nitrate), inflammation (both in brain and ileum myeloperoxidase activity), calcium and blood brain barrier permeability. Treatment with minocycline significantly attenuated prenatal valproic acid induced reduction in social interaction, spontaneous alteration, exploratory activity intestinal motility, serotonin levels and prefrontal cortex mitochondrial complex activity. Furthermore, minocycline has also attenuated prenatal valproic acid induced increase in locomotion, anxiety, brain oxidative and nitrosative stress, inflammation, calcium and blood brain barrier permeability. Thus, it may be concluded that prenatal valproic acid has induced autistic behaviour, biochemistry and blood brain barrier impairment in animals, which were significantly attenuated by minocycline. Minocycline should be explored further for its therapeutic benefits in autism. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/26498253 DOI: https://doi.org/10.1016/j.neuint.2015.10.007  Title(2015): Benefits of agomelatine in behavioral, neurochemical and blood brain barrier alterations in prenatal valproic acid induced autism spectrum disorder.  Valproic acid administration during gestational period causes behavior and biochemical deficits similar to those observed in humans with autism spectrum disorder. Although worldwide prevalence of autism spectrum disorder has been increased continuously, therapeutic agents to ameliorate the social impairment are very limited. The present study has been structured to investigate the therapeutic potential of melatonin receptor agonist, agomelatine in prenatal valproic acid (Pre-VPA) induced autism spectrum disorder in animals. Pre-VPA has produced reduction in social interaction (three chamber social behavior apparatus), spontaneous alteration (Y-Maze), exploratory activity (Hole board test), intestinal motility, serotonin levels (prefrontal cortex and ileum) and prefrontal cortex mitochondrial complex activity (complex I, II, IV). Furthermore, Pre-VPA has increased locomotor activity (actophotometer), anxiety, brain oxidative stress (thiobarbituric acid reactive species, glutathione, and catalase), nitrosative stress (nitrite/nitrate), inflammation (brain and ileum myeloperoxidase activity), calcium levels and blood brain barrier leakage in animals. Treatment with agomelatine has significantly attenuated Pre-VPA induced reduction in social interaction, spontaneous alteration, exploratory activity intestinal motility, serotonin levels and prefrontal cortex mitochondrial complex activity. Furthermore, agomelatine also attenuated Pre-VPA induced increase in locomotion, anxiety, brain oxidative stress, nitrosative stress, inflammation, calcium levels and blood brain barrier leakage. It is concluded that, Pre-VPA has induced autism spectrum disorder, which was attenuated by agomelatine. Agomelatine has shown ameliorative effect on behavioral, neurochemical and blood brain barrier alteration in Pre-VPA exposed animals. Thus melatonin receptor agonists may provide beneficial therapeutic strategy for managing autism spectrum disorder. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/26276454 DOI: https://doi.org/10.1016/j.jams.2015.06.008  Title(2015): Laser Acupuncture Improves Behavioral Disorders and Brain Oxidative Stress Status in the Valproic Acid Rat Model of Autism.  The therapeutic strategy against autism, a severe neurological development disorder, is one of the challenges of this decade. Recent findings show that oxidative stress plays a crucial role on the pathophysiology of autism, and laser acupuncture at Shenmen (HT7) can improve oxidative status in many neurological disorders. Therefore, we aimed to assess the effect of laser acupuncture at HT7 on behavior disorders and oxidative stress status in the cortex, striatum, and hippocampus of the valproic acid rat model of autism. Laser acupuncture was performed once daily during postnatal day (PND) 14-PND 40. Behavioral tests including rotarod, open-field, learning and memory, and social behavior tests were performed during PND 14-PND 40. At the end of study, brain oxidative status including malondialdehyde levels and the activities of superoxide dismutase, catalase, and glutathione peroxidase were determined in the cortex, striatum, and hippocampus. Laser acupuncture at HT7 significantly improved autistic-like behaviors. Decreased malondialdehyde levels were observed in all areas mentioned above, however, increased glutathione peroxidase activity was observed only in the striatum and hippocampus. No changes in superoxide dismutase and catalase activities were observed in any investigated area of the brain. Therefore, our study suggests that laser acupuncture at HT7 partly mitigates autistic-like symptoms via improved oxidative status. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/26264039 DOI: https://doi.org/10.1186/s12906-015-0793-2  Title(2015): Neuroprotective effect of Tagara, an Ayurvedic drug against methyl mercury induced oxidative stress using rat brain mitochondrial fractions.  Methyl mercury (MeHg), an important environmental toxicant is implicated in neurological disorders such as Hunter-Russell syndrome and Autism. Therefore, the present work is in search of new drugs that can alleviate MeHg toxicity. In this connection, Tagara, an ayurvedic drug is used for assessing its neuro protective effect against MeHg toxicity. In the present study, we assessed the phytochemical contents of Tagara by colorimetric and HPLC analyses. The neuroprotective effect of Tagara on MeHg induced neurotoxicity was measured in terms of viability by MTT assay and oxidative stress in terms of catalase activity, glutathione and thiobarbituric acid reactive substance levels. Further, the chelating effect of Tagara towards MeHg was performed to identify the molecular mechanism. Statistical analysis was done by statistical package for social sciences (SPSS) version 16.0. The results demonstrated that Tagara contains significant amounts of phenols and flavonoids. Also, HPLC analysis of Tagara revealed the presence of essential oils such as hydroxyvalerenic and valerenic acids. Our results demonstrated that exposure of rat brain mitochondrial fractions to MeHg resulted in a dose dependent death in MTT assay and IC50 value was found to be 10 μM. However, a 250 μg dose of Tagara effectively prevented MeHg induced mitochondrial damage. The oxidative stress caused by MeHg results in elevated levels of reactive oxygen species as evidenced by elevated TBARS (Thiobarbituric acid-reactive substances) levels and diminished catalase enzyme activity and glutathione content. However, Tagara at 250 μg concentration offsets these alterations caused by MeHg. Further, Tagara also diminished GSH oxidation caused by MeHg, confirming its chelating effect, one of the molecular mechanisms that triggers protection against oxidative damage. Our results revealed that MeHg induced toxicity is predominantly mediated through oxidative stress mechanism and the propensity of Tagara to abolish such reactions. Hence, we propose that Tagara with a source of potential neuroprotectants may be a useful approach to alleviate MeHg associated neurotoxicity. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/25852770 DOI: https://doi.org/10.1186/s13099-015-0054-4  Title(2015): The neurotoxic effects of ampicillin-associated gut bacterial imbalances compared to those of orally administered propionic acid in the etiology of persistent autistic features in rat pups: effects of various dietary regimens.  A healthy gut with normal intestinal microflora is completely disrupted by oral antibiotics. The byproducts of harmful gut bacteria can interfere with brain development and may contribute to autism. Strategies to improve the gut microflora profile through dietary modification may help to alleviate gut disorders in autistic patients. Sixty young male western albino rats were divided into six equal groups. The first group served as the control; the second group was given an oral neurotoxic dose of propionic (PPA) (250 mg/kg body weight/day) for three days. The third group received an orogastric dose of ampicillin (50 mg/kg for three weeks) with a standard diet. Groups 4, 5 and 6 were given an orogastric dose of ampicillin and fed high-carbohydrate, high-protein and high-lipid diets, respectively, for 10 weeks. Biochemical parameters related to oxidative stress were investigated in brain homogenates from each group. The microbiology results revealed descriptive changes in the fecal microbiota of rats treated with ampicillin either alone or with the three dietary regimens. The results of PPA acid and ampicillin treatment showed significant increases in lipid peroxidation and catalase with decreases in glutathione and potassium compared with levels in the control group. A protein-rich diet was effective at restoring the glutathione level, while the carbohydrate-rich diet recovered lipid peroxidation and catalase activity. In addition, the three dietary regimens significantly increase the potassium level in the brain tissue of the test animals. Lactate dehydrogenase was remarkably elevated in all groups relative to the control. No outstanding effects were observed in glutathione S-transferase and creatine kinase. The changes observed in the measured parameters reflect the neurotoxic effects of PPA and ampicillin. Lipid peroxide and catalase activity and the levels of glutathione and potassium are satisfactory biomarkers of PPA and ampicillin neurotoxicity. Based on the effects of the three dietary regimens, a balanced diet can protect against PPA or ampicillin-induced neurotoxicity that might induce autistic traits. These outcomes will help efforts directed at controlling the prevalence of autism, a disorder that has recently been associated with PPA neurotoxicity. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/25732953 DOI: https://doi.org/10.1016/j.bbr.2015.02.041  Title(2015): Astaxanthin improves behavioral disorder and oxidative stress in prenatal valproic acid-induced mice model of autism.  Prenatal exposure to valproic acid on gestational day 12.5 may lead to the impaired behavior in the offspring, which is similar to the human autistic symptoms. To the contrary, astaxanthin shows neuroprotective effect by its antioxidant mechanism. We aimed to (i) develop mice model of autism and (ii) investigate the effect of astaxanthin on such model animals. Valproic acid (600 mg/kg) was administered intraperitoneally to the pregnant mice on gestational day 12.5. Prenatal valproic acid-exposed mice were divided into 2 groups on postnatal day 25 and astaxanthin (2mg/kg) was given to the experimental group (VPA\_AST, n=10) while saline was given to the control group (VPA, n=10) for 4 weeks. Behavioral test including social interaction, open field and hot-plate were conducted on postnatal day 25 and oxidative stress markers such as lipid peroxidation, advanced protein oxidation product, nitric oxide, glutathione, and activity of superoxide dismutase and catalase were estimated on postnatal day 26 to confirm mice model of autism and on postnatal day 56 to assess the effect of astaxanthin. On postnatal day 25, prenatal valproic acid-exposed mice exhibited (i) delayed eye opening (ii) longer latency to respond painful stimuli, (iii) poor sociability and social novelty and (iv) high level of anxiety. In addition, an increased level of oxidative stress was found by determining different oxidative stress markers. Treatment with astaxanthin significantly (p<0.05) improved the behavioral disorder and reduced the oxidative stress in brain and liver. In conclusion, prenatal exposure to valproic day in pregnant mice leads to the development of autism-like features. Astaxanthin improves the impaired behavior in animal model of autism presumably by its antioxidant activity. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/25673846 DOI: https://doi.org/10.1523/JNEUROSCI.2778-14.2015  Title(2015): Dysregulation of glutamine transporter SNAT1 in Rett syndrome microglia: a mechanism for mitochondrial dysfunction and neurotoxicity.  Rett syndrome (RTT) is an autism spectrum disorder caused by loss-of-function mutations in the gene encoding MeCP2, an epigenetic modulator that binds the methyl CpG dinucleotide in target genes to regulate transcription. Previously, we and others reported a role of microglia in the pathophysiology of RTT. To understand the mechanism of microglia dysfunction in RTT, we identified a MeCP2 target gene, SLC38A1, which encodes a major glutamine transporter (SNAT1), and characterized its role in microglia. We found that MeCP2 acts as a microglia-specific transcriptional repressor of SNAT1. Because glutamine is mainly metabolized in the mitochondria, where it is used as an energy substrate and a precursor for glutamate production, we hypothesize that SNAT1 overexpression in MeCP2-deficient microglia would impair the glutamine homeostasis, resulting in mitochondrial dysfunction as well as microglial neurotoxicity because of glutamate overproduction. Supporting this hypothesis, we found that MeCP2 downregulation or SNAT1 overexpression in microglia resulted in (1) glutamine-dependent decrease in microglial viability, which was corroborated by reduced microglia counts in the brains of MECP2 knock-out mice; (2) proliferation of mitochondria and enhanced mitochondrial production of reactive oxygen species; (3) increased oxygen consumption but decreased ATP production (an energy-wasting state); and (4) overproduction of glutamate that caused NMDA receptor-dependent neurotoxicity. The abnormalities could be rectified by mitochondria-targeted expression of catalase and a mitochondria-targeted peptide antioxidant, Szeto-Schiller 31. Our results reveal a novel mechanism via which MeCP2 regulates bioenergetic pathways in microglia and suggest a therapeutic potential of mitochondria-targeted antioxidants for RTT. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/23840462 DOI: https://doi.org/10.1371/journal.pone.0066418  Title(2013): Oxidative Stress and Erythrocyte Membrane Alterations in Children with Autism: Correlation with Clinical Features.  It has been suggested that oxidative stress may play a role in the pathogenesis of Autism Spectrum Disorders (ASD), but the literature reports somewhat contradictory results. To further investigate the issue, we evaluated a high number of peripheral oxidative stress parameters, and some related issues such as erythrocyte membrane functional features and lipid composition. Twenty-one autistic children (Au) aged 5 to 12 years, were gender and age-matched with 20 typically developing children (TD). Erythrocyte thiobarbituric acid reactive substances, urinary isoprostane and hexanoyl-lysine adduct levels were elevated in Au, thus confirming the occurrence of an imbalance of the redox status of Au, whilst other oxidative stress markers or associated parameters (urinary 8-oxo-dG, plasma radical absorbance capacity and carbonyl groups, erythrocyte superoxide dismutase and catalase activities) were unchanged. A very significant reduction of Na(+)/K(+)-ATPase activity (-66%, p<0.0001), a reduction of erythrocyte membrane fluidity and alteration in erythrocyte fatty acid membrane profile (increase in monounsaturated fatty acids, decrease in EPA and DHA-ω3 with a consequent increase in ω6/ω3 ratio) were found in Au compared to TD, without change in membrane sialic acid content. Some Au clinical features appear to be correlated with these findings; in particular, hyperactivity score appears to be related with some parameters of the lipidomic profile and membrane fluidity. Oxidative stress and erythrocyte membrane alterations may play a role in the pathogenesis of ASD and prompt the development of palliative therapeutic protocols. Moreover, the marked decrease in NKA could be potentially utilized as a peripheral biomarker of ASD. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/23607226 DOI: NA  Title(2013): Blood lipid peroxidation, antioxidant enzyme activities and hemorheological changes in autistic children.  Early infantile autism is a severe form of childhood psychiatric disease with characteristic symptoms. Hyperserotoninaemia in 43.5%, lactic acidosis 43% and hyperpyruvataemia in 30% were biochemically demonstrated in autistic children. Our earlier results led to the postulation that a dissequilibrium in the blood redox is involved in infantile autism; the oxidative loading and the antioxidant defending enzyme system were investigated together with the hemorheological parameters in infantile autism. Malonyl-dialdehyde (MDA) endproduct of lipid peroxidation and activities of the antioxidant enzymes: superoxide dismutase (SOD), catalase (C-ase), glutathione peroxidase (GP-ase) and reduced glutathione (GSH) were biochemically determined from plasma and red blood cells. The antioxidant specificities were investigated in plasma and red blood cell haemolysate from 25 infantile autistic children. Significantly increased superoxide dismutase (SOD) (2.89 vs. 1.32 U/mg protein, p < 0.01) and decreased glutathione peroxidase (0.620 vs. 0.910 U/mg protein, p < 0.01) levels as well as catalase (0.463 vs. 4.948 BU/mg protein, p < 0.001) activities were detected; while the plasma and erythrocyte lipid peroxidation and the reduced glutathione (GSH) levels did not change. The results of the investigated prooxidant and the antioxidant status provide evidence that there exists an oxidative stress in children with infantile autism. While investigating the hemorheological parameters of 25 infantile autistic patients, some characteristic pathological parameters were detected: the initial filtration rate (Fi) (0.72 vs. 0.75 p < 0.01) and the clogging rate (CR) (1.926 vs. 2.912, p < 0.01) values of red blood cells (RBC) decreased while the mean transit time (Tc) (8.93 vs. 7.39, p < 0.001) increased suggesting reduced RBC deformability. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/22708999 DOI: https://doi.org/10.2174/092986712802002572  Title(2012): Glutathione-related factors and oxidative stress in autism, a review.  Autism spectrum disorders are complex neuro-developmental disorders whose neurobiology is proposed to be associated with oxidative stress which is induced by reactive oxygen species. The process of oxidative stress can be a target for therapeutic interventions. In this study, we aimed to review the role of oxidative stress, plasma glutathione (GSH), and related factors as the potential sources of damage to the brain as well as the possible related factors which reduce the oxidative stress. Methylation capacity, sulfates level, and the total glutathione level are decreased in autism. On the other hand, both oxidized glutathione and the ratio of oxidized to reduced glutathione are increased in autism. In addition, the activity of glutathione peroxidase, superoxide dismutase, and catalase, as a part of the antioxidative stress system are decreased. The current literature suggests an imbalance of oxidative and anti-oxidative stress systems in autism. Glutathione is involved in neuro-protection against oxidative stress and neuro-inflammation in autism by improving the anti-oxidative stress system. Decreasing the oxidative stress might be a potential treatment for autism. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/22542447 DOI: https://doi.org/10.1016/j.freeradbiomed.2012.03.011  Title(2012): Oxidative stress-related biomarkers in autism: systematic review and meta-analyses.  Autism spectrum disorders (ASDs) are rarely diagnosed in children younger than 2 years, because diagnosis is based entirely on behavioral tests. Oxidative damage may play a central role in this pathogenesis, together with the interconnected transmethylation cycle and transsulfuration pathway. In an attempt to clarify and quantify the relationship between oxidative stress-related blood biomarkers and ASDs, a systematic literature review was carried out. For each identified study, mean biomarker levels were compared in cases and controls providing a point estimate, the mean ratio, for each biomarker. After meta-analysis, the ASD patients showed decreased blood levels of reduced glutathione (27%), glutathione peroxidase (18%), methionine (13%), and cysteine (14%) and increased concentrations of oxidized glutathione (45%) relative to controls, whereas superoxide dismutase, homocysteine, and cystathionine showed no association with ASDs. For the C677T allele in the methylene tetrahydrofolate reductase gene (MTHFR), homozygous mutant subjects (TT) showed a meta-OR of 2.26 (95% CI 1.30-3.91) of being affected by ASD with respect to the homozygous nonmutant (CC). Case-control studies on blood levels of vitamins suggest a lack of association (folic acid and vitamin B12) or rare association (vitamins A, B6, C, D, E). Sparse results were available for other biomarkers (ceruloplasmin, catalase, cysteinylglycine, thiobarbituric acid-reactive substances, nitric oxide) and for polymorphisms in other genes. Existing evidence is heterogeneous and many studies are limited by small sample size and effects. In conclusion, existing evidence suggests a role for glutathione metabolism, the transmethylation cycle, and the transsulfuration pathway, although these findings should be interpreted with caution, and larger, more standardized studies are warranted. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/22531301 DOI: https://doi.org/10.1186/1742-2094-9-74  Title(2012): Etiology of autistic features: the persisting neurotoxic effects of propionic acid.  Recent clinical observations suggest that certain gut and dietary factors may transiently worsen symptoms in autism. Propionic acid (PA) is a short chain fatty acid and an important intermediate of cellular metabolism. Although PA has several beneficial biological effects, its accumulation is neurotoxic. Two groups of young Western albino male rats weighing about 45 to 60 grams (approximately 21 days old) were used in the present study. The first group consisted of oral buffered PA-treated rats that were given a neurotoxic dose of 250 mg/kg body weight/day for three days, n = eight; the second group of rats were given only phosphate buffered saline and used as a control. Biochemical parameters representing oxidative stress, energy metabolism, neuroinflammation, neurotransmission, and apoptosis were investigated in brain homogenates of both groups. Biochemical analyses of brain homogenates from PA-treated rats showed an increase in oxidative stress markers (for example, lipid peroxidation), coupled with a decrease in glutathione (GSH) and glutathione peroxidase (GPX) and catalase activities. Impaired energy metabolism was ascertained through the decrease of lactate dehydrogenase and activation of creatine kinase (CK). Elevated IL-6, TNFα, IFNγ and heat shock protein 70 (HSP70) confirmed the neuroinflammatory effect of PA. Moreover, elevation of caspase3 and DNA fragmentation proved the pro-apoptotic and neurotoxic effect of PA to rat pups By comparing the results obtained with those from animal models of autism or with clinical data on the biochemical profile of autistic patients, this study showed that the neurotoxicity of PA as an environmental factor could play a central role in the etiology of autistic biochemical features. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/22322665 DOI: https://doi.org/10.1007/s11064-012-0717-1  Title(2012): Bacopa monniera (L.) Wettst ameliorates behavioral alterations and oxidative markers in sodium valproate induced autism in rats.  Early prenatal or post natal exposure to environmental insults such as valproic acid (VPA), thalidomide and ethanol could induce behavioral alterations similar to autistic symptoms. Bacopa monniera, a renowned plant in ayurvedic medicine is useful in several neurological disorders. The purpose of the present study was to evaluate the effect of B. monniera on VPA induced autism. On 12.5 day of gestation the female pregnant rats were divided into control and VPA treated groups. They were administered saline/VPA (600 mg/kg, i.p.) respectively and allowed to raise their own litters. Group I-male pups of saline treated mothers. On postnatal day (PND) 21 VPA induced autistic male pups were divided into two groups (n = 6); Group II-received saline and Group III-received B. monniera (300 mg/kg/p.o.) from PND 21-35. Behavioral tests (nociception, locomotor activity, exploratory activity, anxiety and social behavior) were performed in both adolescence (PND 30-40) and adulthood (PND 90-110) period. At the end of behavioral testing animals were sacrificed, brain was isolated for biochemical estimations (serotonin, glutathione, catalase and nitric oxide) and histopathological examination. Induction of autism significantly affected normal behavior, increased oxidative stress and serotonin level, altered histoarchitecture of cerebellum (decreased number of purkinje cells, neuronal degeneration and chromatolysis) when compared with normal control group. Treatment with B. monniera significantly (p < 0.05) improved behavioral alterations, decreased oxidative stress markers and restored histoarchitecture of cerebellum. In conclusion, the present study suggests that B. monniera ameliorates the autistic symptoms possibly due to its anti-anxiety, antioxidant and neuro-protective activity. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/22249148 DOI: https://doi.org/10.1016/j.cbpc.2012.01.003  Title(2012): Valproate-induced teratogenesis in Japanese rice fish (Oryzias latipes) embryogenesis.  Fertilized eggs of Japanese rice fish (medaka) at three developmental stages (Iwamatsu stages 4-30) were exposed to waterborne valproic acid (VPA) (0-80 mM) in hatching solution for 48 h. The amount of valproate to cause 50% mortality (IC(50)) is found to be developmental stage-specific. The embryos were more sensitive to valproate at early stages of development (Iwamatsu stages 4-10) than in the embryos in late stages (Iwamatsu stages 17-30). Valproate exposed embryos have microcephaly and disrupted cardiovasculature with delayed vessel circulation, thrombus formation, and slow heart rate. The hatching efficiency is also reduced by valproate exposure due to developmental delay. The mRNA analysis of nine genes belong to oxidative stress (catalase, gsr, gst), neurogenesis (iro3, wnt1, shh, otx2, nlgn3b) and cell cycle regulation (ccna2) have been done. It was observed that the genes belong to oxidative stress remained unaltered after valproate exposure. However, some of the genes belong to neurogenesis (wnt1,shh, otx2 and nlgn3b) and cell cycle (ccna2) showed developmental stage-specific alteration after valproate exposure. This study indicates that valproate is able to induce some of the phenotypic features which are analogous to human fetal valproate syndrome (FVS). Modulation of genes expressed in neural tissues indicates that this fish can be used to analyze the mechanisms of many neurobehavioral disorders like Autism spectrum disorder (ASD) in human. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/22225920 DOI: https://doi.org/10.1016/j.jpsychires.2011.10.004  Title(2012): Plasma antioxidant capacity is reduced in Asperger syndrome.  Recent evidence suggests that children with autism have impaired detoxification capacity and may suffer from chronic oxidative stress. To our knowledge, there has been no study focusing on oxidative metabolism specifically in Asperger syndrome (a milder form of autism) or comparing this metabolism with other psychiatric disorders. In this study, total antioxidant status (TAOS), non-enzymatic (glutathione and homocysteine) and enzymatic (catalase, superoxide dismutase, and glutathione peroxidase) antioxidants, and lipid peroxidation were measured in plasma or erythrocyte lysates in a group of adolescent patients with Asperger syndrome, a group of adolescents with a first episode of psychosis, and a group of healthy controls at baseline and at 8-12 weeks. TAOS was also analyzed at 1 year. TAOS was reduced in Asperger individuals compared with healthy controls and psychosis patients, after covarying by age and antipsychotic treatment. This reduced antioxidant capacity did not depend on any of the individual antioxidant variables measured. Psychosis patients had increased homocysteine levels in plasma and decreased copper and ceruloplasmin at baseline. In conclusion, Asperger patients seem to have chronic low detoxifying capacity. No impaired detoxifying capacity was found in the first-episode psychosis group in the first year of illness. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/19306862 DOI: https://doi.org/10.1016/j.clinbiochem.2009.03.011  Title(2009): Metabolic biomarkers related to oxidative stress and antioxidant status in Saudi autistic children.  Measurement of oxidative stress and antioxidant-related parameters (enzymatic and non-enzymatic) in Saudi autistic children. 30 autistic children (22 males and 8 females) aged 3-15 years (25/30 of these were below 8 years old), and 30 healthy children as control group were included in this study. Levels of lipid peroxides, vitamin E, vitamin C, glutathione together with enzymatic activities of glutathione peroxidase (GSH-Px), and catalase were determined in plasma while superoxide dismutase (SOD was measured in red blood cells of both groups. Lipid peroxidation was found to be significantly higher in autistic compared to control Saudi children. On the other hand, vitamin E and glutathione were remarkably lower in autistic patients while vitamin C shows non-significant lower values. Regarding the enzymatic antioxidants, both glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) were significantly higher in autistic compared to control while catalase recorded more or less similar activities in both groups. Saudi autistic children are under H(2)O(2) stress due to GSH depletion, over expression of SOD together with the unchanged catalase enzyme. This could be helpful in the early diagnosis of young autistic patients and suggesting the possibility of antioxidant supplementation for the early intervention with autistic children. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/16766163 DOI: https://doi.org/10.1016/j.pathophys.2006.05.007  Title(2006): Oxidative stress in autism.  Autism is a severe developmental disorder with poorly understood etiology. Oxidative stress in autism has been studied at the membrane level and also by measuring products of lipid peroxidation, detoxifying agents (such as glutathione), and antioxidants involved in the defense system against reactive oxygen species (ROS). Lipid peroxidation markers are elevated in autism, indicating that oxidative stress is increased in this disease. Levels of major antioxidant serum proteins, namely transferrin (iron-binding protein) and ceruloplasmin (copper-binding protein), are decreased in children with autism. There is a positive correlation between reduced levels of these proteins and loss of previously acquired language skills in children with autism. The alterations in ceruloplasmin and transferrin levels may lead to abnormal iron and copper metabolism in autism. The membrane phospholipids, the prime target of ROS, are also altered in autism. The levels of phosphatidylethanolamine (PE) are decreased, and phosphatidylserine (PS) levels are increased in the erythrocyte membrane of children with autism as compared to their unaffected siblings. Several studies have suggested alterations in the activities of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase in autism. Additionally, altered glutathione levels and homocysteine/methionine metabolism, increased inflammation, excitotoxicity, as well as mitochondrial and immune dysfunction have been suggested in autism. Furthermore, environmental and genetic factors may increase vulnerability to oxidative stress in autism. Taken together, these studies suggest increased oxidative stress in autism that may contribute to the development of this disease. A mechanism linking oxidative stress with membrane lipid abnormalities, inflammation, aberrant immune response, impaired energy metabolism and excitotoxicity, leading to clinical symptoms and pathogenesis of autism is proposed. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/36945527 DOI: https://doi.org/10.1101/2023.03.07.531534  Title(2023): TAD Evolutionary and functional characterization reveals diversity in mammalian TAD boundary properties and function.  Topological associating domains (TADs) are self-interacting genomic units crucial for shaping gene regulation patterns. Despite their importance, the extent of their evolutionary conservation and its functional implications remain largely unknown. In this study, we generate Hi-C and ChIP-seq data and compare TAD organization across four primate and four rodent species, and characterize the genetic and epigenetic properties of TAD boundaries in correspondence to their evolutionary conservation. We find that only 14% of all human TAD boundaries are shared among all eight species (ultraconserved), while 15% are human-specific. Ultraconserved TAD boundaries have stronger insulation strength, CTCF binding, and enrichment of older retrotransposons, compared to species-specific boundaries. CRISPR-Cas9 knockouts of two ultraconserved boundaries in mouse models leads to tissue-specific gene expression changes and morphological phenotypes. Deletion of a human-specific boundary near the autism-related AUTS2 gene results in upregulation of this gene in neurons. Overall, our study provides pertinent TAD boundary evolutionary conservation annotations, and showcase the functional importance of TAD evolution. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/35589920 DOI: https://doi.org/10.1007/s12035-022-02860-0  Title(2022): Differential Regulation of Mouse Hippocampal Gene Expression Sex Differences by Chromosomal Content and Gonadal Sex.  Common neurological disorders, like Alzheimer's disease (AD), multiple sclerosis (MS), and autism, display profound sex differences in prevalence and clinical presentation. However, sex differences in the brain with health and disease are often overlooked in experimental models. Sex effects originate, directly or indirectly, from hormonal or sex chromosomal mechanisms. To delineate the contributions of genetic sex (XX v. XY) versus gonadal sex (ovaries v. testes) to the epigenomic regulation of hippocampal sex differences, we used the Four Core Genotypes (FCG) mouse model which uncouples chromosomal and gonadal sex. Transcriptomic and epigenomic analyses of ~ 12-month-old FCG mouse hippocampus, revealed genomic context-specific regulatory effects of genotypic and gonadal sex on X- and autosome-encoded gene expression and DNA modification patterns. X-chromosomal epigenomic patterns, classically associated with X-inactivation, were established almost entirely by genotypic sex, independent of gonadal sex. Differences in X-chromosome methylation were primarily localized to gene regulatory regions including promoters, CpG islands, CTCF binding sites, and active/poised chromatin, with an inverse relationship between methylation and gene expression. Autosomal gene expression demonstrated regulation by both genotypic and gonadal sex, particularly in immune processes. These data demonstrate an important regulatory role of sex chromosomes, independent of gonadal sex, on sex-biased hippocampal transcriptomic and epigenomic profiles. Future studies will need to further interrogate specific CNS cell types, identify the mechanisms by which sex chromosomes regulate autosomes, and differentiate organizational from activational hormonal effects. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/35379308 DOI: https://doi.org/10.1186/s13041-022-00916-9  Title(2022): CTCF in parvalbumin-expressing neurons regulates motor, anxiety and social behavior and neuronal identity.  CCCTC-binding factor (CTCF) is a regulator of chromatin organization and has direct effects on gene transcription. Mutations in CTCF have been identified in individuals with neurodevelopmental conditions. There are wide range of behaviors associated with these mutations, including intellectual disabilities, changes in temperament, and autism. Previous mice-model studies have identified roles for CTCF in excitatory neurons in specific behaviors, particularly in regards to learning and memory. However, the role of CTCF in inhibitory neurons is less well defined. In the current study, specific knockout of CTCF in parvalbumin-expressing neurons, a subset of inhibitory neurons, induced a specific behavioral phenotype, including locomotor abnormalities, anxiolytic behavior, and a decrease in social behavior. The anxiolytic and social abnormalities are detected before the onset of locomotor abnormalities. Immunohistochemical analysis revealed a disbalance in parvalbumin-expressing and somatostatin-expressing cells in these mice. Single nuclei RNA sequencing identified changes in gene expression in parvalbumin-expressing neurons that are specific to inhibitory neuronal identity and function. Electrophysiology analysis revealed an enhanced inhibitory tone in the hippocampal pyramidal neurons in knockout mice. These findings indicate that CTCF in parvalbumin-expressing neurons has a significant role in the overall phenotype of CTCF-associated neurodevelopmental deficits. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/33004838 DOI: https://doi.org/10.1038/s41467-020-18723-y  Title(2020): Large-scale targeted sequencing identifies risk genes for neurodevelopmental disorders.  Most genes associated with neurodevelopmental disorders (NDDs) were identified with an excess of de novo mutations (DNMs) but the significance in case-control mutation burden analysis is unestablished. Here, we sequence 63 genes in 16,294 NDD cases and an additional 62 genes in 6,211 NDD cases. By combining these with published data, we assess a total of 125 genes in over 16,000 NDD cases and compare the mutation burden to nonpsychiatric controls from ExAC. We identify 48 genes (25 newly reported) showing significant burden of ultra-rare (MAF < 0.01%) gene-disruptive mutations (FDR 5%), six of which reach family-wise error rate (FWER) significance (p < 1.25E-06). Among these 125 targeted genes, we also reevaluate DNM excess in 17,426 NDD trios with 6,499 new autism trios. We identify 90 genes enriched for DNMs (FDR 5%; e.g., GABRG2 and UIMC1); of which, 61 reach FWER significance (p < 3.64E-07; e.g., CASZ1). In addition to doubling the number of patients for many NDD risk genes, we present phenotype-genotype correlations for seven risk genes (CTCF, HNRNPU, KCNQ3, ZBTB18, TCF12, SPEN, and LEO1) based on this large-scale targeted sequencing effort. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/30377227 DOI: https://doi.org/10.1523/JNEUROSCI.3496-17.2018  Title(2019): CTCF Governs the Identity and Migration of MGE-Derived Cortical Interneurons.  The CCCTC-binding factor (CTCF) is a central regulator of chromatin topology recently linked to neurodevelopmental disorders such as intellectual disability, autism, and schizophrenia. The aim of this study was to identify novel roles of CTCF in the developing mouse brain. We provide evidence that CTCF is required for the expression of the LIM homeodomain factor LHX6 involved in fate determination of cortical interneurons (CINs) that originate in the medial ganglionic eminence (MGE). Conditional Ctcf ablation in the MGE of mice of either sex leads to delayed tangential migration, abnormal distribution of CIN in the neocortex, a marked reduction of CINs expressing parvalbumin and somatostatin (Sst), and an increased number of MGE-derived cells expressing Lhx8 and other markers of basal forebrain projection neurons. Likewise, Ctcf-null MGE cells transplanted into the cortex of wild-type hosts generate fewer Sst-expressing CINs and exhibit lamination defects that are efficiently rescued upon reexpression of LHX6. Collectively, these data indicate that CTCF regulates the dichotomy between Lhx6 and Lhx8 to achieve correct specification and migration of MGE-derived CINs.SIGNIFICANCE STATEMENT This work provides evidence that CCCTC-binding factor (CTCF) controls an early fate decision point in the generation of cortical interneurons mediated at least in part by Lhx6. Importantly, the abnormalities described could reflect early molecular and cellular events that contribute to human neurological disorders previously linked to CTCF, including schizophrenia, autism, and intellectual disability. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/29133437 DOI: https://doi.org/10.1523/JNEUROSCI.0936-17.2017  Title(2018): Abnormal Microglia and Enhanced Inflammation-Related Gene Transcription in Mice with Conditional Deletion of Ctcf in Camk2a-Cre-Expressing Neurons.  CCCTC-binding factor (CTCF) is an 11 zinc finger DNA-binding domain protein that regulates gene expression by modifying 3D chromatin structure. Human mutations in CTCF cause intellectual disability and autistic features. Knocking out Ctcf in mouse embryonic neurons is lethal by neonatal age, but the effects of CTCF deficiency in postnatal neurons are less well studied. We knocked out Ctcf postnatally in glutamatergic forebrain neurons under the control of Camk2a-Cre. CtcfloxP/loxP;Camk2a-Cre+ (Ctcf CKO) mice of both sexes were viable and exhibited profound deficits in spatial learning/memory, impaired motor coordination, and decreased sociability by 4 months of age. Ctcf CKO mice also had reduced dendritic spine density in the hippocampus and cerebral cortex. Microarray analysis of mRNA from Ctcf CKO mouse hippocampus identified increased transcription of inflammation-related genes linked to microglia. Separate microarray analysis of mRNA isolated specifically from Ctcf CKO mouse hippocampal neurons by ribosomal affinity purification identified upregulation of chemokine signaling genes, suggesting crosstalk between neurons and microglia in Ctcf CKO hippocampus. Finally, we found that microglia in Ctcf CKO mouse hippocampus had abnormal morphology by Sholl analysis and increased immunostaining for CD68, a marker of microglial activation. Our findings confirm that Ctcf KO in postnatal neurons causes a neurobehavioral phenotype in mice and provide novel evidence that CTCF depletion leads to overexpression of inflammation-related genes and microglial dysfunction.SIGNIFICANCE STATEMENT CCCTC-binding factor (CTCF) is a DNA-binding protein that organizes nuclear chromatin topology. Mutations in CTCF cause intellectual disability and autistic features in humans. CTCF deficiency in embryonic neurons is lethal in mice, but mice with postnatal CTCF depletion are less well studied. We find that mice lacking Ctcf in Camk2a-expressing neurons (Ctcf CKO mice) have spatial learning/memory deficits, impaired fine motor skills, subtly altered social interactions, and decreased dendritic spine density. We demonstrate that Ctcf CKO mice overexpress inflammation-related genes in the brain and have microglia with abnormal morphology that label positive for CD68, a marker of microglial activation. Our findings suggest that inflammation and dysfunctional neuron-microglia interactions are factors in the pathology of CTCF deficiency. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/22395465 DOI: https://doi.org/10.4161/epi.7.2.18910  Title(2012): Epigenetic and genetic variation at the IGF2/H19 imprinting control region on 11p15.5 is associated with cerebellum weight.  IGF2 is a paternally expressed imprinted gene with an important role in development and brain function. Allele-specific expression of IGF2 is regulated by DNA methylation at three differentially methylated regions (DMRs) spanning the IGF2/H19 domain on human 11p15.5. We have comprehensively assessed DNA methylation and genotype across the three DMRs and the H19 promoter using tissue from a unique collection of well-characterized and neuropathologically-dissected post-mortem human cerebellum samples (n = 106) and frontal cortex samples (n = 51). We show that DNA methylation, particularly in the vicinity of a key CTCF-binding site (CTCF3) in the imprinting control region (ICR) upstream of H19, is strongly correlated with cerebellum weight. DNA methylation at CTCF3 uniquely explains ~25% of the variance in cerebellum weight. In addition, we report that genetic variation in this ICR is strongly associated with cerebellum weight in a parental-origin specific manner, with maternally-inherited alleles associated with a 16% increase in cerebellum weight compared with paternally-inherited alleles. Given the link between structural brain abnormalities and neuropsychiatric disease, an understanding of the epigenetic and parent-of-origin specific genetic factors associated with brain morphology provides important clues about the etiology of disorders such as schizophrenia and autism. |
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| Url: https://pubmed.ncbi.nlm.nih.gov/21725066 DOI: https://doi.org/10.1093/hmg/ddr298  Title(2011): Neuron-specific impairment of inter-chromosomal pairing and transcription in a novel model of human 15q-duplication syndrome.  Although the etiology of autism remains largely unknown, cytogenetic and genetic studies have implicated maternal copy number gains of 15q11-q13 in 1-3% of autism cases. In order to understand how maternal 15q duplication leads to dysregulation of gene expression and altered chromatin interactions, we used microcell-mediated chromosome transfer to generate a novel maternal 15q duplication model in a human neuronal cell line. Our 15q duplication neuronal model revealed that by quantitative RT-PCR, transcript levels of NDN, SNRPN, GABRB3 and CHRNA7 were reduced compared with expected levels despite having no detectable alteration in promoter DNA methylation. Since 15q11-q13 alleles have been previously shown to exhibit homologous pairing in mature human neurons, we assessed homologous pairing of 15q11-q13 by fluorescence in situ hybridization. Homologous pairing of 15q11-q13 was significantly disrupted by 15q duplication. To further understand the extent and mechanism of 15q11-q13 homologous pairing, we mapped the minimal region of homologous pairing to a ∼500 kb region at the 3' end of GABRB3 which contains multiple binding sites for chromatin regulators MeCP2 and CTCF. Both active transcription and the chromatin factors MeCP2 and CTCF are required for the homologous pairing of 15q11-q13 during neuronal maturational differentiation. These data support a model where 15q11-q13 genes are regulated epigenetically at the level of both inter- and intra-chromosomal associations and that chromosome imbalance disrupts the epigenetic regulation of genes in 15q11-q13. |