Robert NAVIAUX, *et al.*
Suramin vs Autism

https://health.ucsd.edu/news/topics/suramin-autism/pages/default.aspx

Suramin and Autism

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Suramin is a 100-year-old drug developed to treat African sleeping sickness and river blindness. Though it has been investigated for other diseases, including cancer, it is not approved for any therapeutic use in the United States.

However, a small, randomized clinical trial conducted by Robert Naviaux, MD, PhD , professor of medicine, pediatrics and pathology, and colleagues at University of California San Diego School of Medicine have found that a single intravenous dose of suramin produced dramatic, but transient, improvement of core symptoms of autism spectrum disorder (ASD). Currently, there are no drugs approved for treating the core symptoms of ASD.

More broadly, the trial findings support the “cell danger response theory,” which posits that autism and other chronic conditions are fundamentally driven by metabolic dysfunction—and thus treatable. Naviaux and his co-authors propose larger, longer clinical trials to assess suramin (or similar drugs) as an ASD treatment.

Special note from the researchers: Suramin is not approved for the treatment of autism. Like many intravenous drugs, when administered improperly by untrained personnel, at the wrong dose and schedule, without careful measurement of drug levels and monitoring for toxicity, suramin can cause harm. Careful clinical trials will be needed over several years at several sites to learn how to use low-dose suramin safely in autism, and to identify drug-drug interactions and rare side effects that cannot currently be predicted. We strongly caution against the unauthorized use of suramin.

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https://health.ucsd.edu/news/topics/suramin-autism/pages/q-and-a.aspx

Q&A: Suramin Autism Treatment-1 (SAT-1) Trial

Interview with Robert Naviaux, MD, PhD, professor of genetics in the departments of medicine, pediatrics and pathology

QUESTION: What is the main point of your paper?
ANSWER: The first thing you need to know about our paper is that it is not about suramin. Our research is aimed at finding a unifying cause for autism and an explanation for why it, and nearly 20 other chronic diseases, have been increasing over the past 30 years. Our research is leading us to the conclusion that autism is caused by a treatable metabolic syndrome in many children. The exact percentage is currently unknown. Metabolism is the language the brain, gut and immune system use to communicate. These three systems are linked. You can't change one without changing the other. Each of these systems works differently in autism, but more specifically, the communication between these systems is changed in autism. Such changes occur both during and after the pregnancy. Suramin can only improve metabolic functions once a child is treated. While antipurinergic therapy (APT) with suramin may not directly change some aspects of abnormal brain development that were present before treatment, APT may improve the function of many brain systems, even if brain structure does not change. And in children and teens whose brains are still developing, the course or trajectory of brain development might also be changed by treatment.

The metabolic syndrome that underlies the dysfunction is caused by the abnormal persistence of the cell danger response or CDR. Aspects of the CDR are also known to scientists as the "integrated stress response." Both genes and environment contribute to the CDR, so even genetic causes of autism lower the threshold for CDR activation and produce the metabolic syndrome. Ultimately, if the symptoms of autism are caused by a metabolic syndrome, the hopeful message is that the symptoms can be treated, even though we can't change the genes.

QUESTION:What can you say about the study for neuroscientists and families who have never heard of the cell danger response or purinergic signaling?
ANSWER: The main conclusions from the study do not require any background knowledge. Although the study was small and preliminary, the main conclusions were three: 1) For many children, the symptoms of autism are not fixed and can be

improved dramatically with the right treatment; 2) A treatable metabolic syndrome contributes to the pathogenesis of core symptoms of autism and 3) A single treatment with low-dose suramin was safe and produced significant improvements in the core symptoms and metabolism associated with ASD.

QUESTION: What are the caveats?
ANSWER: After summarizing the design and results of the study, we are left with the conclusion that either the results are wrong because of the small size of the study, or they are an important advance. We won't know which until the results can be replicated in larger studies. Even so, I am optimistic that we are on the right path. My hope is that other investigators will soon join in. Together we can all move faster to prove or disprove the CDR hypothesis and test the safety and efficacy of antipurinergic therapy in autism.

QUESTION. What exactly is the cell danger response (CDR)?
ANSWER: The CDR is a natural and universal cellular response to any injury or stress. Its purpose is to help protect the cell and to jump-start the healing process. But sometimes the CDR gets stuck. This prevents completion of the natural healing cycle and can permanently alter the way the cell responds to the world. When this happens, cells behave as if they are still injured or in imminent danger, even though the original cause of the injury or threat has passed. On a molecular level, the defended set points for cellular homeostasis are altered. This creates a pathological metabolic memory—an abnormal cellular response—that leads to chronic disease. When this happens during early child development, it causes autism and many other chronic childhood disorders. When it happens later in life, a persistent CDR can lead to immune exhaustion and it can lower the resistance to chronic infections. When it swings in the other direction, the immune system takes on a hair trigger and it leads to inflammatory and autoimmune disorders. In both cases, it increases the prevalence of chronic disease.

QUESTION: How is purinergic signaling connected to the CDR?
ANSWER: In a second discovery from the lab, we found that extracellular nucleotide signaling called "purinergic signaling" maintains the CDR. This led us to the possibility of a unified approach to the treatment of autism. Antipurinergic drugs can treat the abnormal metabolic syndrome that causes autism by sending a cellular "all's clear" or safety signal like the one that is announced when a fire is extinguished, telling you it is safe to return to school. Suramin is just the oldest antipurinergic drug available, and the only one that inhibits the particular purinergic receptors that cause autism. Many more antipurinergic drugs are in development. Suramin is just the first of a whole new class of medicines, like the first statin for high cholesterol or the first beta blocker for high blood pressure.

QUESTION: How does suramin work?
ANSWER: Pharmacologically, suramin has several actions. One of its best-studied actions is as an inhibitor of purinergic signaling. Inside the cell, nucleotides like ATP and UTP are energy carriers and important molecules in normal metabolism. Stressed cells release ATP and other molecules made by mitochondria into the extracellular space through channels in the cell membrane. Extracellular ATP (eATP) is an ancient danger signal. It is called a "damage associated molecular pattern" or DAMP. When too much eATP is released, it binds to purinergic receptors and activates the CDR. Suramin inhibits the binding of eATP and eADP to these receptors and sends the cellular equivalent of the "all's clear" or safety signal. In this capacity, suramin and other antipurinergic drugs are a kind of molecular armistice therapy, signaling the cellular war is over, the danger has passed and cells can return to "peacetime" jobs like normal neurodevelopment, growth, and healing.

Clinically, suramin works by removing negative signals that block or slow natural child development. It is more like removing the brakes then pressing the accelerator. Accelerated catch-up development occurs in the first few weeks when the brakes are removed because the child is ready to develop, but was otherwise blocked by their illness. This reminds me of giving a child who has an inborn error of metabolism in a vitamin or nutrient that they can't make or taking away a toxin. The children begin to blossom. Children with severe oral motor dyspraxia in the SAT-1 study started humming and singing nonsense tunes around the house in the first few days after suramin. Like a baby learning to talk for the first time, they began making new sounds with their mouth, lips and tongue that they had never made before. We had four non-verbal children in the study, two 6-year-olds and the two 14-year-olds. The 6- and the 14-year-old who received suramin said the first sentences of their lives about one week after the single suramin infusion. This did not happen in any of the children given placebo.

QUESTION: How many purinergic receptors are there?
ANSWER: There are 19 different purinergic receptors. Geoff Burnstock (University College London) discovered purinergic signaling in 1972, and has been characterizing the nucleotide and nucleoside ligands, their receptors and their biology ever since.

QUESTION: What about the side effects of suramin?
ANSWER: We did not find any serious side effects or safety concerns in this first study of a single, low-dose of suramin. The low dose that we used produced blood levels of 5-15 μM and has never been tested for any disease in the nearly 100 years that suramin has been used in medicine. All previous uses of suramin have been at medium doses for sleeping sickness that produced blood levels of 50-100 μM for one to three months or high doses for cancer chemotherapy that produced blood levels of 150-270 μM for three to six months.

It is important to remember that our study was small and only five boys received suramin. We were unable to detect rare side effects that might affect fewer than twenty percent (1 in 5) patients. Suramin caused a self-limited, asymptomatic rash, but this disappeared without treatment in two to four days. Larger clinical trials will be needed to detect uncommon side effects. For example, a study in which at least 100 children received suramin would be necessary to detect a side effect that occurred in just one out of 100 (1 percent) of children.

QUESTION: What about the risk of infections? If suramin blocks the CDR, won't children have trouble clearing common infections or responding to toxin exposures?
ANSWER: In theory, this could be a risk of suramin. However, we looked at this carefully in the trial. The infusions were done from October through February, so winter colds were a known risk. We found that two children in the placebo group got colds. Two children in the suramin group also had colds. The severity was the same in both groups. The duration of congestion and symptoms was seven to 10 days, and also about the same in both groups. We did not find an increased risk of infection in the SAT-1 study. However, in theory, any broad-spectrum antipurinergic drug might inhibit the CDR so this will be a potential risk to monitor in future studies.

QUESTION: What problems can you imagine that might derail future suramin trials in autism?
ANSWER: If the improvements that occurred with suramin treatment stopped after a few months, even when effective blood levels were maintained, then the trials would fail. Also, if we encountered a safety issue that was unacceptable after a few months of treatment, then the trials might fail.

Even if suramin itself is not the best antipurinergic drug for autism, our studies have helped blaze the trail for the development of new antipurinergic drugs that might be even better. Before our work, no one knew that purinergic signaling abnormalities were a part of autism. Now we do, and new drugs can be developed rationally and systematically.

QUESTION: Will suramin need to be given for life?
ANSWER: I don't think so, but we don't have the science to answer this question yet. More studies will be necessary to see if improved development can become self-sustaining without the need for regular suramin treatment.

QUESTION: What about the effect that suramin might have on common therapies?
ANSWER: We found that during the time the children were on suramin, the benefit from all their usual therapies and enrichment programs increased dramatically. Once suramin removed the roadblocks to development, the benefit from speech therapy, occupational therapy, applied behavior analysis and even from playing games with other children during recess at school skyrocketed. Suramin was synergistic with their other therapies.

QUESTION: Why was your study so small?
ANSWER: This work is new and this type of clinical trial is expensive. We did not have enough funding to do a larger study. And even with the funding we were able to raise, we had to go $500,000 in debt to complete the SAT-1 trial. Fortunately, the goals of establishing basic safety, tolerability and activity of suramin in autism were accomplished with just 10 subjects. Based on these initial promising results, we will now attempt to find funding for a larger trial.

QUESTION: What is the rate-limiting factor to progress right now? Where are the bottlenecks?
ANSWER: The rate-limiting factor is money. Lack of funding has slowed our research progress on the CDR and purinergic signaling in autism for the past nine years. We can't do the next studies without new funding. We have plans for five additional studies over the next five years to collect all the data the FDA will need to decide about the approval of suramin for autism. With adequate funding, culminating in a multicenter, phase III, registrational trial, these studies can be completed without further delay. Usually, the multimillion dollar cost of new drug development is covered by the Big Pharma that will benefit from FDA approval. Unfortunately, since suramin is 100 years old, the usual patent laws don't apply and the next clinical trials will require grass roots support from families and foundations and other approaches to raise the needed funding. There's more information at our website: http://naviauxlab.ucsd.edu/ .

QUESTION: Do you think that suramin could help the genetic causes of autism too? Why?
ANSWER: Yes. Each of the genes that increase the risk of autism is connected to the cell danger response. For example, the Fragile X gene naturally prevents the translation of a large number of pro-inflammatory proteins. When the Fragile X gene is mutant, pro-inflammatory proteins like TNF-alpha and IL1-beta are made, which activates the CDR. The causal gene in Angelman syndrome is thought to be the ubiquitin protein ligase E3A (UBE3A). When this gene is not expressed, worn-out proteins in the cell are not removed properly. This triggers the unfolded protein response, which activates the CDR. The causal gene in Smith-Magenis syndrome is thought to be the retinoic acid activated gene 1 (RAI), which is needed for a normal antiviral response. Failure to express RAI prevents normal handling of infections and results in a persistently activated CDR. We don't think that suramin will treat the physical features and non-autism symptoms of these genetic disorders. However, we think that suramin will be effective in improving the core symptoms of autism in these genetic disorders, and produce improvements in language, social behavior, and decrease repetitive and restricted behaviors.

QUESTION: What about teens and adults with ASD who don't want to be treated but rather want to be accepted and appreciated for their unique talents, abilities, and differences?
ANSWER: ASD is a label we use to talk about a group of children and adults with a recognizable pattern of neurodevelopmental differences. In the extreme, some non-verbal children with ASD will grow up to be non-verbal adults who cannot speak for themselves and may not ever be able to care for their own daily needs or hold down jobs.

In the other extreme, the special gifts of some children with ASD will lead them to become activists as teens and adults whose voices are highly sought out by local and national agencies to express the needs of others and to help guide progress. We had a gifted teen with ASD as part of the team on the SAT1 study. He is a graphic artist and helped us to design the storyboards that allowed each parent and their child to visually review and prepare for the steps of the study, with special attention to sensory issues that were important for children with ASD.

I have no desire to create new treatments for anyone who does not need or want treatment. I do not want to eliminate any

symptoms or special gifts that someone wants to keep. The right to self-determination and the right to health care choice are fundamental freedoms. However, unless research can continue with the goal of helping children and adults who want treatment, new treatments will not be discovered and the complementary freedom to choose a treatment when it is desired will be lost. We can respect both rights: the right to choose no treatment for some and the right to choose new treatments for others. Both are possible, and both must be actively chosen to protect freedoms for all.

There is another point that needs to be made. In 2017, after more than 70 years of trying, there are no effective pharmacologic treatments for the core symptoms of autism because a unifying theory for the cause of autism does not exist. People's experience with ASD treatments-to-date have taught them that the treatment is often worse than the disorder. None of the treatments currently available actually get at the root problem in autism. If the root problem is ultimately proven to be the CDR and abnormalities in purinergic signaling, then the core symptoms like social fear, anxiety and difficulties with verbal communication might be improved without suppressing the gifts that make children and adults with ASD exceptional. This new generation of treatments has a chance to precisely target the symptoms that hold people back with ASD, while not touching the gifts that allow them to excel.

QUESTION: Why is treating autism so important?
ANSWER: Autism spectrum disorder often affects children who have shown early gifts, and might otherwise grow up to become some of the best and brightest of their generation. Even if this is only true for a fraction of children, it means that some children now living with disabling forms of ASD, whose parents fear they might never be able to live independently, could have a chance for independence and live happy, self-reliant lives. And because many children with ASD are significantly impacted by their symptoms, these children, once freed from their most disabling symptoms, might be just the ones the world needs to solve the greatest problems facing our planet in the next century.

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https://www.jbiomeds.com/biomedical-sciences/antipurinergic-therapy-with-suramin-as-a-treatment-for-autism-spectrum-disorder.php?aid=8945

Antipurinergic Therapy with Suramin as a Treatment for Autism Spectrum Disorder
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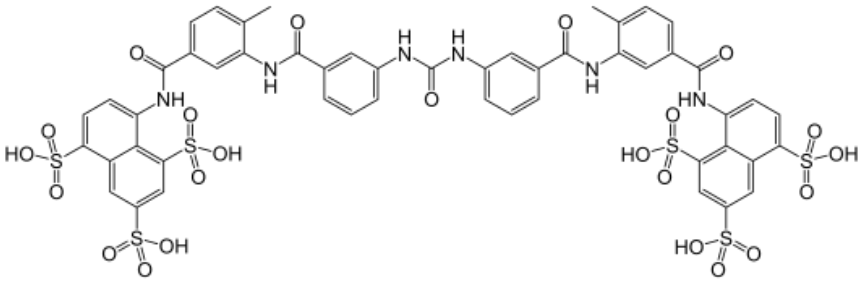
https://en.wikipedia.org/wiki/Suramin

Suramin



Trade names : Antrypol, 309 Fourneau, Bayer 205, others
Routes of administration : by injection only
ATC code P01CX02 (WHO) QP51AE02 (WHO)
Legal status: US: not FDA approved
CAS Number : 145-63-1 ☑
ECHA InfoCard 100.005.145 Edit this at Wikidata
Chemical and physical data
Formula C51H40N6O23S6
Molar mass : 1297.26 g·mol−1

Suramin is a medication used to treat African sleeping sickness and river blindness.[1][2] It is the treatment of choice for sleeping sickness without central nervous system involvement.[3] It is given by injection into a vein.[4]

Suramin causes a fair number of side effects.[4] Common side effects include nausea, vomiting, diarrhea, headache, skin tingling, and weakness.[2] Sore palms of the hands and soles of the feet, trouble seeing, fever, and abdominal pain may also

occur.[2] Severe side effects may include low blood pressure, decreased level of consciousness, kidney problems, and low blood cell levels.[4] It is unclear if it is safe when breastfeeding.[2]

Suramin was made at least as early as 1916.[5] It is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system.[6] In the United States it can be acquired from the Center for Disease Control (CDC).[3] The cost of the medication for a course of treatment is about US$27.[7] In regions of the world where the disease is common suramin is provided for free by the World Health Organization (WHO).[8]"

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http://naviauxlab.ucsd.edu/science-item/autism-research/

Autism Research

Our lab sees autism spectrum disorder (ASD) as an involuntary behavioral syndrome caused by a conserved cellular response to environmental and genetic danger. Autism is therefore an "ecogenetic" syndrome that alters child development. This perspective has led us to a unified theory for the cause and treatment of ASD that is called the cell danger theory1-7. It proposes that autism is a treatable metabolic syndrome caused by persistent activation of the cell danger response (CDR) produced by persistent abnormalities in purinergic signaling.

By treating the root cause of this syndrome, we believe many children will have chance to lose the symptoms that hold them back. Many children will be able to come off spectrum, and many children will be able to live independent lives as adults, when just a few years ago this notion seemed impossible...

WO2018013811
DIAGNOSTIC AND METHODS OF TREATMENT FOR CHRONIC FATIGUE SYNDROME AND AUTISM SPECTRUM DISORDERS
[PDF]

Abstract
The disclosure relates to biomarkers useful for diagnosing and predicting the development of chronic fatigue syndrome (CFS). The disclosure further provides methods to reset metabolism and facilitate healing in CFS patients by administering antipurinergic compounds.

WO2018148580
METHODS FOR AUTISM SPECTRUM DISORDER PHARMACOTHERAPY
[PDF]

Abstract
Disclosed herein are compositions of antipurinergic agents and methods of use thereof for treating cognitive developmental disorders and autism spectrum disorders (ASD) in patients in need thereof.

US2004224920
Methods of treatment of mitochondrial disorders
[PDF]

Abstract
In accordance with the present invention, there are provided methods for the treatment of mitochondrial disorders. Invention methods include the administration of a pyrimidine-based nucleoside such as triacetyluridine, or the like. Also provided are methods of reducing or eliminating symptoms associated with mitochondrial disorders. Mitochondrial disorders particularly appropriate for treatment include those attributable to a deficiency of one or more pyrimidines.

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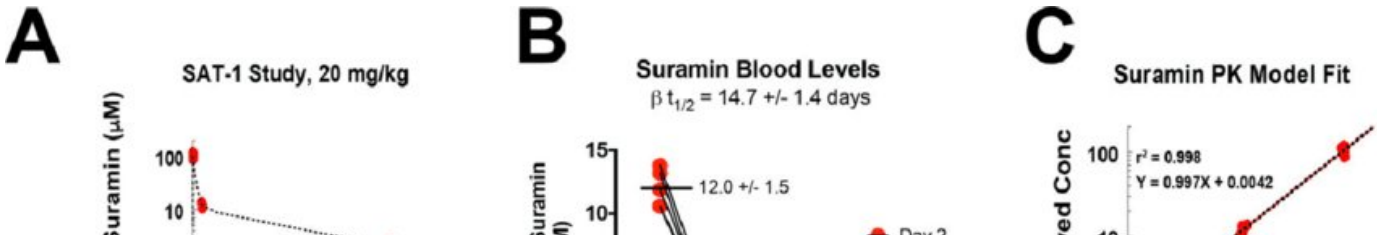
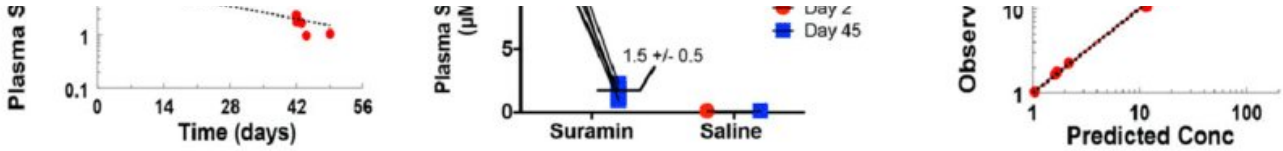
https://www.researchgate.net/figure/Pharmacokinetics-of-single-dose-suramin-in-children-with-autism-spectrum-disorders-A_fig3_318135634

Pharmacokinetics of single-dose suramin in children with autism ...





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Parameter	Symbol	Mean ± sd
Beta elimination half-life	$t_{1/2}\,\beta$	14.7 ± 1.4 days
Alpha elimination half-life	$t_{1/2}\,\alpha$	7.41 ± 0.55 hours
Clearance	CL	1.95 ± 0.21 mL/hr/kg
Steady state volume of distribution	Vd_{ss}	0.83 ± 0.014 L/kg

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https://www.ncbi.nlm.nih.gov/pubmed/23516405
PLoS One. 2013;8(3):e57380. doi: 10.1371/journal.pone.0057380. Epub 2013 Mar 13.

Antipurinergic therapy corrects the autism-like features in the poly(IC) mouse model.
Naviaux RK, et al.

Abstract
BACKGROUND: Autism spectrum disorders (ASDs) are caused by both genetic and environmental factors. Mitochondria act to connect genes and environment by regulating gene-encoded metabolic networks according to changes in the chemistry of the cell and its environment. Mitochondrial ATP and other metabolites are mitokines-signaling molecules made in mitochondria-that undergo regulated release from cells to communicate cellular health and danger to neighboring cells via purinergic signaling. The role of purinergic signaling has not yet been explored in autism spectrum disorders.
OBJECTIVES AND METHODS: We used the maternal immune activation (MIA) mouse model of gestational poly(IC) exposure and treatment with the non-selective purinergic antagonist suramin to test the role of purinergic signaling in C57BL/6J mice.
RESULTS: We found that antipurinergic therapy (APT) corrected 16 multisystem abnormalities that defined the ASD-like phenotype in this model. These included correction of the core social deficits and sensorimotor coordination abnormalities, prevention of cerebellar Purkinje cell loss, correction of the ultrastructural synaptic dysmorphology, and correction of the hypothermia, metabolic, mitochondrial, P2Y2 and P2X7 purinergic receptor expression, and ERK1/2 and CAMKII signal transduction abnormalities.
CONCLUSIONS: Hyperpurinergia is a fundamental and treatable feature of the multisystem abnormalities in the poly(IC) mouse model of autism spectrum disorders. Antipurinergic therapy provides a new tool for refining current concepts of pathogenesis in autism and related spectrum disorders, and represents a fresh path forward for new drug development.

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https://www.ncbi.nlm.nih.gov/pubmed/25705365
Mol Autism. 2015 Jan 13;6:1.
doi: 10.1186/2040-2392-6-1

Antipurinergic therapy corrects the autism-like features in the Fragile X (Fmr1 knockout) mouse model.
Naviaux JC, et al.

Abstract
BACKGROUND: This study was designed to test a new approach to drug treatment of autism spectrum disorders (ASDs) in the Fragile X (Fmr1) knockout mouse model.
METHODS: We used behavioral analysis, mass spectrometry, metabolomics, electron microscopy, and western analysis to test the hypothesis that the disturbances in social behavior, novelty preference, metabolism, and synapse structure are treatable with antipurinergic therapy (APT).
RESULTS: Weekly treatment with the purinergic antagonist suramin (20 mg/kg intraperitoneally), started at 9 weeks of age, restored normal social behavior, and improved metabolism, and brain synaptosomal structure. Abnormalities in synaptosomal glutamate, endocannabinoid, purinergic, and IP3 receptor expression, complement C1q, TDP43, and amyloid β precursor protein (APP) were corrected. Comprehensive metabolomic analysis identified 20 biochemical pathways associated with symptom improvements. Seventeen pathways were shared with human ASD, and 11 were shared with the maternal immune activation (MIA) model of ASD. These metabolic pathways were previously identified as functionally related mediators of the evolutionarily conserved cell danger response (CDR).
CONCLUSIONS: The data show that antipurinergic therapy improves the multisystem, ASD-like features of both the environmental MIA, and the genetic Fragile X models. These abnormalities appeared to be traceable to mitochondria and

regulated by purinergic signaling.

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https://www.ncbi.nlm.nih.gov/pubmed/24937094
Transl Psychiatry. 2014 Jun 17;4:e400.
doi: 10.1038/tp.2014.33.

Reversal of autism-like behaviors and metabolism in adult m ice with single-dose antipurinergic therapy.

Naviaux JC, et al.

Abstract
Autism spectrum disorders (ASDs) now affect 1-2% of the children born in the United States. Hundreds of genetic, metabolic and environmental factors are known to increase the risk of ASD. Similar factors are known to influence the risk of schizophrenia and bipolar disorder; however, a unifying mechanistic explanation has remained elusive. Here we used the maternal immune activation (MIA) mouse model of neurodevelopmental and neuropsychiatric disorders to study the effects of a single dose of the antipurinergic drug suramin on the behavior and metabolism of adult animals. We found that disturbances in social behavior, novelty preference and metabolism are not permanent but are treatable with antipurinergic therapy (APT) in this model of ASD and schizophrenia. A single dose of suramin (20 mg kg(-1) intraperitoneally (i.p.)) given to 6-month-old adults restored normal social behavior, novelty preference and metabolism. Comprehensive metabolomic analysis identified purine metabolism as the key regulatory pathway. Correction of purine metabolism normalized 17 of 18 metabolic pathways that were disturbed in the MIA model. Two days after treatment, the suramin concentration in the plasma and brainstem was 7.64 μM pmol μl(-1) (±0.50) and 5.15 pmol mg(-1) (±0.49), respectively. These data show good uptake of suramin into the central nervous system at the level of the brainstem. Most of the improvements associated with APT were lost after 5 weeks of drug washout, consistent with the 1-week plasma half-life of suramin in mice. Our results show that purine metabolism is a master regulator of behavior and metabolism in the MIA model, and that single-dose APT with suramin acutely reverses these abnormalities, even in adults.

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https://www.ncbi.nlm.nih.gov/pubmed/29253638
Mitochondrion. 2018 Nov;43:1-15.
doi: 10.1016/j.mito.2017.12.007

Antipurinergic therapy for autism-An in-depth review.

Naviaux RK

Abstract
Are the symptoms of autism caused by a treatable metabolic syndrome that traces to the abnormal persistence of a normal, alternative functional state of mitochondria? A small clinical trial published in 2017 suggests this is possible. Based on a new unifying theory of pathogenesis for autism called the cell danger response (CDR) hypothesis, this study of 10 boys, ages 5-14years, showed that all 5 boys who received antipurinergic therapy (APT) with a single intravenous dose of suramin experienced improvements in all the core symptoms of autism that lasted for 5-8weeks. Language, social interaction, restricted interests, and repetitive movements all improved. Two children who were non-verbal spoke their first sentences. None of these improvements were observed in the placebo group. Larger and longer studies are needed to confirm this promising discovery. This review introduces the concept of M2 (anti-inflammatory) and M1 (pro-inflammatory) mitochondria that are polarized along a functional continuum according to cell stress. The pathophysiology of the CDR, the complementary functions of M1 and M2 mitochondria, relevant gene-environment interactions, and the metabolic underpinnings of behavior are discussed as foundation stones for understanding the improvements in ASD behaviors produced by antipurinergic therapy in this small clinical trial.

GB729847A

A new diamidine salt and process for its preparation

[PDF]

The invention comprises the salt of the symmetrical urea of m-aminobenzoyl-p-methyl-m - aminobenzoyl - 1 - aminonaphthalene-4 : 6 : 8-trisulphonic acid (suramin) and 1 : 5-di - (41 - amidinophenoxy) pentane uncontaminated with either the acid or the base from which it may be formed or another salt of said base or said acid. It can be produced by reacting in aqueous medium a water-soluble salt of the suramin (e.g. the sodium salt) with a water-soluble salt, such as the isethionate or methane sulphonate, of the 1 : 5-di-(41-amidinophenoxy) pentane and isolating from the reaction medium the diamidine salt thus formed. An example illustrates this process.

The diamidine salt of this invention is prepared by reaction together in an aqueous medium a water-soluble salt, for example, the sodium salt of the symmetrical urea of m-aminobenzoyl-pmethyl - m - aminobenzoyl - 1 - aminonaphthalene 4:6:8-trisulphonic acid, which urea is hereinafter referred to by its common name "suramin," and a water-soluble salt of 1:5-di(4-amidinophenoxy)pentane, for example, the isethionate or methane sulphonate, and isolating from the reaction mixture the salt thus formed. The resulting salt is <RTI>enly</RTI> sparingly soluble in <RTI>water,</RTI> and is <RTI>conveniently isolated by crystallisation.

The salt as thus; prepared has been</RTI> proved to bel of <RTI>considerable</RTI> <RTI>value</RTI> as a therapeutic

agent. More particularly, it has been shown to possess a marked prophylactic and curative effect in the treatment of trypanosome infections. Both 1:5-di(4-amidinophenoxy)-pentane and suramin are known to possess in the form of certain water-soluble salts, such as the isethionate and sodium salts respectively trypanocidal activity but comparative experiments have demonstrated the fact (which is all the more surprising in view of the low solubility of the suramin salt of the diamidine) that the new salt is unexpectedly and substantially superior to either. Thus, in parallel toxicity experiments in rats to determine the maximum non-lethal dose on sub-cutaneous administration, the following figures were obtained:
(a) 1:5-di(4-amidino-phenoxy-pentane 5 mg./100 g.
(b) suramin - - - - - - - 40 mg./100 g.
(c) the suramin salt of the diamidine > 500 mg./100 g.

The diamidine itself is known to possess a prophylactic action against rat trypanosomiasis and comparative tests of the diamidine and the new salt thereof were therefore conducted in this <RTI>connec</RTI> tion. In these tests the drugs were administered sub-cutaneously and after definite intervals (1, 2, 4, 8 and 12 weeks) the test animals were inoculated subcutaneously with the aforesaid strain of T. brucel and the blood examined every two or three days for a month. If in that period no evidence of infection was found protection was considered complete. Ubder these test conditions, it was found that the diamidine at maximum non-lethal dose (5 mg./100 g.) gave protection for 4 weeks while the new salt at less than one thirtieth of the maximum non-lethal dose (15 mg./100 g.) gave protection for at least 8 months.

Further, such <RTI>tests</RTI> in which all three <RTI>products were compared showed that the</RTI> maximum doses requireld to give com<RTI>plete</RTI> protection for a period of 4 <RTI>weeks</RTI> were 5 mg./100 g. in the case of the diamidine, 2 mg/100 g. in the case of suramin and 1.96 mg./100 g. of the new salt containing 0.7 mg. of the diamidine <RTI>and O.S mg. of surarain.</RTI>

The <RTI>production</RTI> of the <RTI>new</RTI> salt is illustrated in tbe following Example,

EXAMPLE.
To a solution of suramin sodium (14.3 g.) in water (30 c.c.) is added a solution of 1:5 - di(4-amidinophenoxy)-pentane methane-sulphonate in water (300 c.c.) at 45 C. A white precipitate forms which is left to stand overnight and is then filtered off, washed with water (150 c.c.) and dried at 50 C. under 12 mm. of mercury. The suramin salt of 1:5di(4-amidinophenoxy)-pentane (26 g.) is thus obtained which crystallises with 30 molecules of water.

We are aware that Guimares and Lourie, British Journal of Pharmacology and Chemotherapy (1951) Vol. 6, pages 514 to 530, have referred to the fact that a precipitate is liable to form in mixtures of dilute solutions of suramin and 1:5-di(4-amidinophenoxy)pentanealso known as pentamidine and give reasons for attributing to the formation of an inactive salt complex the inhibitory effect observed by them in respect of a previous injection of suramin (or the presence of suramin) on certain actions of pentamidine, viz, fall of blood pressure, broncho-constriction, contraction of gut, " curare-like " action on the rat phrenic nerve diaphragm preparation, paralysis in frogs and toxicity for mice.

GB862345A
Improvements in or relating to heterocyclic compounds
[PDF]

This invention is for improvements in or relating to phenanthridinium salts and to processes for their production, and has for its object the provision of new and therapeutically useful substances.

While many phenanthridine compounds, in the form of their quaternary salts, have heretofore been proposed for use as trypanocidal agents, only a few have been used to any substantial extent in the field. Not only degree of activity but also toxicity vary markedly with change in the number and nature of substituents and it is impossible at the present time to predict a priori the properties (if any) of any new phenanthridine compound.

As a result of research and experimentation, the present Applicants have prepared new phenanthridinium salts which have a high activity against blood parasites, such as trypanosomes, are surprisingly less toxic than Inown phenanthridinium salts possessing useful trypanocidal activity and, in consequence, exhibit an exceptionally high chemotherapeutic index.

The marked utility of the new compounds is manifested not only in the treatment of trypanosome infections but also in relation to babesiasis.,,

According to a further feature of the invention, those salts of formula I in which R1 represents a hydrogen atom or a m amidinophenyldiazoamino group, may be prepared by diazotizing or tetrazctizing a phenanthridinium salt of formula II wherein R is a hydrogen atom or an amino group and coupling the resultant diazonium or bisdiazonium salt with m-aminobenzamidine,
The invention is illustrated by the following Examples, in which the temperatures stated were measured in degrees Centigrade.

EXAMPLE I
A solution of m-aminobenzamidine monohydrochloride dihydrate (51.9 g.) in water (225 ml.) and concentrated hydrochloric acid (56.5 ml.) was cooled to 0 and diazotised with sodium nitrite (17.6 g.) in water (100 ml.) any excess nitrous acid

remaining being decomposed by the addition of sulphamic acid. The diazonium solution was added to a solution of 2:7 - diamino - 10 - ethyl9-phenylphenanthridinium chloride (99.5 g.) in water (600 ml.) at 00. To the stirred mixture, an ice-cold solution of sodium acetate (142.5 g.) in water (450 ml.) was added.

Stirring was continued at 0 for 75 minutes and then a further quantity of sodium acetate (61.5 g.) together with sodium chloride (45 g.) dissolved in ice-cold water (450 ml.) was added. After 45 minutes the product was precipitated as a purple tar by the addition of saturated brine (600 ml.). The supernatant liquors were decanted. The purple residue was dissolved in water (1 1.) and reprecipitated with brine (500 ml.). Paper electrophoresis of the precipitated tar (No.1 Whatman paper" Whatman" is a Registered Trade Mark) in 3N acetic acid showed the presence of two main components, the more mobile one giving a purple spot, the less mobile one giving a yellow spot. Subsequent purification steps were followed by paper electrophoresis; the purple isomer isolated was found to correspond to the purple spot and the red isomer to the yellow spot.

The presence of traces of unchanged 2:7 diamino - 10 - ethyl - 9 - phenylphenanthrdinium chloride in the unpurified reaction product was indicated, on paper electrophoresis, by the presence of a characteristic orange spot. The foregoing precipitated tar was dissolved in boiling water (300 ml.) andthe solution rapidly cooled. The solid A which separated on standing in the refrigerator overnight was filtered off from the liquors R. On crystallisation of the solid A by dissolving it in boiling water and rapidly cooling the solution purple prisms, m.p. 258260 (decomp.) were obtained.

To the liquors B, obtained as described above, saturated sodium bromide solution was added. The solid precipitate (60 g.) was washed with acetone and extracted with cold methanol (5 x 100 ml.) to leave a red residue (24.3 g., 15.5%) which was shown by paper electrophoresis to be an almost pure product. Crystallisation of this product from methanol gave 7 - (m - amidinophenyl diazeamino) - 2 - amino - 10 - ethyl-9-phenyl- phenanthridinium bromide hydrobromide as red needles, m.p. 2400 (decomp.).

This bromide hydrobromide salt (1 g.) in methanol (700 ml.) was converted to the corresponding chloride hydrochloride by ion exchange through a column of Axnberlite IRA 400 ("Arnberlite" is a Registered Trade Mark) chloride resin. 7 - (m - Amidino phenyldiazoamino) - 2 - amino - 10 - ethyl 9 - phenylphenanthridinium chloride hydro chloride was obtained as red needles, m.p.
244-245 (decomp.)...

GB901643A
Phenanthridinium salts and their preparation
[PDF]

Abstract
The invention comprises: (a) amidinophenyldiazoaminophenanthridinium salts of the general formula (wherein Am represents -C(:NH)NH2, R1 a C1-6 alkyl group, R2 an aryl group, R3 a C1-6 alkoxy group or a halogen atom and Y a pharmaceutically acceptable anion) and their acid addition salts (including insoluble salts, e.g. amsonates, embonates and suramin salts); (b) the preparation of compounds I, in admixture with isomeric azo dyestuffs (see Group IV(c)) from which they may or may not be separated, by diazotizing a compound of the general formula and coupling the resulting diazonium salt with an equimolecular proportion of a phenanthridinium salt of the general formula and (c) pharmaceutical compositions comprising at least one compound I, with or without the isomeric azo dyestuff, in association with a significant amount of a pharmaceutical carrier. Compounds I can also be prepared by diazotizing a compound III and coupling the resulting diazonium salt with a compound II. The pharmaceutical compositions, which are active against blood parasites, e.g. trypano somes, may be in forms suitable for parenteral or oral administration, e.g. solutions, suspensions, emulsions, tablets, pills, dispersible powders, granules, syrups, elixirs and capsules. 4 - Amino-3-bromobenzamidine monohydrochloride, 3-amino - 4 - chlorobenzamidine dihydrochloride and 3-amino-4-methoxybenzamidine dihydrochloride are prepared from the correspondingly substituted benzonitriles. 3-Amino-4-chlorobenzonitrile is prepared by reducing 4-chloro-3-nitrobenzonitrile.ALSO:Azo dyestuffs of the general formula (wherein R1 represents a C1-6 alkyl group, R2 represents an aryl group, Y represents an anion, one Z represents the group and the others hydrogen atoms, Am represents -C(:NH)NH2 and R3 represents a C1-6 alkoxy group or a halogen atom) are obtained as by-products in the preparation of diazoamino compounds (see Group IV(b)) by diazotizing a compound of the general formula and coupling the resulting diazonium salt with an equimolecular proportion of a phenanthridinium salt of the general formula The two products may be separated by, for example, fractional crystallization from methanol.
