variations in integrin alphav expression is strongly correlated with immobility time in the FST.
Conclusions: Taken together, our data reveals a significant *Slc6a4* x *Itgb3* genetic interaction in the modulation of serotonin homeostasis in the central nervous system. Altered 5-HT homeostasis likely arises from the functional interaction between integrin alphavbeta3 and SERT, which may modulate 5-HT transport capacity in serotonergic synapses. Our data also suggests separate, but related, mechanisms modifying anxiety and depressive-like behaviors. Both anxiety- and depressive behaviors depend on *Slc6a4* haploinsufficiency, but we observed significant alterations in depression tests only in the context of *Itgb3* haploinsufficiency. We suspect that these behaviors are associated with integrin alphavbeta3-dependent changes in neuronal structure and function, likely through the modulation of other neurotransmitter systems, as neurogenesis or immobility times did not follow the normalization of serotonin homeostasis by chronic citalopram treatment. Finally, linear regression revealed that immobility time is correlated with integrin alphav expression, a measure modified by Slc6a4 haploinsufficiency. Therefore, integrin alphavbeta3 is a novel modulator of neurogenesis and depression in the central nervous system. As *ITGB3* is a highly polymorphic gene, it may significantly contribute to risk for mood and anxiety disorders, especially in the context of *SLC6A4* haploinsufficiency.
Keywords: depression, genetic interaction, integrin, serotonin, transporter.
Disclosures: S. Varney, Nothing to Disclose; A. Whyte, Nothing to Disclose; T. Jessen, Nothing to Disclose; A. Carneiro, Nothing to Disclose.

T8. Dopamine-Independent Motor Control and Hyperactivity Involving Acetylcholine Systems

Kazutaka Ikeda*, Yoko Hagino, Shinya Kasai

Addictive Substance Project, Tokyo, Japan

Background: The disruption of dopamine (DA) systems has been implicated in major neurological and psychiatric disorders, including Parkinson's disease (PD) and schizophrenia. However, effective movement in patients with Parkinson's disease in certain situations, kinesia paradoxa, and typical antipsychotic-resistant and atypical antipsychotic-sensitive positive symptoms of schizophrenia and their underlying mechanisms remain to be elucidated.
Methods: The experimental procedures and housing conditions were approved by the Institutional Animal Care and Use Committee (Animal Experimentation Ethics Committee of Tokyo Metropolitan Institute of Medical Science, Approval ID: 12–43), and all of the animals were cared for and treated humanely in accordance with our institutional animal experimentation guidelines. Dopamine-deficient (DD) mice were generated using a transgenic rescue approach, in which tyrosine hydroxylase (TH) expression in noradrenergic and adrenergic cells in mice that lack TH expression was complemented by a specific DA β-hydroxylase gene promoter. These mice exhibited a restoration of norepinephrine (NE) and epinephrine synthesis and prevention of the usual perinatal lethality and cardiac dysfunction observed in TH knockout mice. Dopamine, serotonin, NE, and acetylcholine (ACh) concentrations in brain microdialysates were determined by high-performance liquid chromatography with electrochemical detection (HTEC-500, Eicom, Kyoto, Japan). Locomotor activity was measured with Supermex (Muromachi Kikai, Tokyo, Japan) and a sensor monitor mounted above the chamber. After a 180 min habituation period, the drugs were administered subcutaneously, and locomotor activity was monitored continuously for 180 min. The mice walked freely on the runway, and their locomotor movements were recorded at 200 frames per second using a high-speed digital image camera system (HAS-220, DITECT, Tokyo, Japan). Movement analyses were limited to the sagittal plane parallel to the direction of walking. Custom-designed image analysis software (DIPP-Motion 2D, DITECT, Tokyo, Japan) was used to extract the two-dimensional coordinates of the various joint markers and reconstruct a stick diagram representation of the right hindlimb. The expression profiles of the genes related to ACh metabolism and signaling transduction pathways were analyzed using the Illumina iScan system with MouseRef-8 Expression BeadChips (Illumina, San Diego, CA, USA), which contain probes that detect over 24 000 transcripts. Immunoblot analysis and immunohistochemistry were also performed.
Results: The present study showed that DD mice can move effectively and are rather hyperactive. DD mice require daily administration of L-dihydroxyphenylalanine (L-DOPA), the precursor of DA, to maintain feeding. After 3 days withdrawal from L-DOPA, their striatal extracellular DA levels fell to less than 0.2% of wildtype mice, and they were hyperactive with a slight movement disorder in a novel environment. The atypical antipsychotic drug clozapine markedly ameliorated this hyperactivity, with no effect of the typical antipsychotic drug haloperidol. Furthermore, the nonselective muscarinic ACh receptor agonist oxotremorine-M and ACh esterase inhibitor donepezil blocked hyperactivity in DD mice. These mice exhibited a reduction of choline acetyltransferase (ChAT) gene and protein expression in the basal ganglia and a reduction of extracellular ACh levels in the striatum, suggesting that reduced cholinergic function may underlie hyperactivity in DD mice.
Conclusions: The DD mice in the present study revealed a novel motor-control and hyperactivity mechanism that is independent of DA and involves ACh systems. The activity of ChAT has been found to be normal or reduced in the striatum in PD patients. Furthermore, the basal ganglia are interconnected with the pedunculopontine nucleus (PPN). The PPN is thought to be involved in the initiation and modulation of gait and other stereotyped movements. In PD patients, the loss of cholinergic neurons in the PPN has been reported. The decrease in dopaminergic neuronal transmission in the basal ganglia might result in the inactivation of the PPN in PD patients and DD mice. The present results, together with previous findings, suggest that the ACh systems may be involved in the mechanisms that underlie DA-independent motor control, and motor impairment in PD patients may be ameliorated by DA-independent mechanisms. Although DA plays a prominent role in the pathogenesis and treatment of schizophrenia, several lines of evidence suggest an important role for the

cholinergic system in the pathophysiology of schizophrenia. Hyperactivity induced by muscarinic receptor antagonists has been suggested to model antimuscarinic psychosis and cholinergic-related psychosis in schizophrenia. Hyperactivity in DD mice was ameliorated by a muscarinic receptor agonist in the present study, suggesting that such hyperactivity may be induced by similar mechanisms that underlie cholinergic-related psychosis in schizophrenia. DD mice might be useful for the identification of the neuronal mechanisms involved in cholinergic-related psychosis in schizophrenia.

Keywords: dopamine, atypical antipsychotic drug, clozapine, motor control, acetylcholine.

Disclosures: K. Ikeda, Nothing to Disclose; Y. Hagino, Nothing to Disclose; S. Kasai, Nothing to Disclose.

T9. A New Model for Studying Effects of Witnessing Traumatic Events in Rats

Samina Salim*, Gaurav Patki, Naimesh Solanki, Farida Allam, Amber Ansari

University of Houston, Houston, Texas

Background: Post-traumatic stress disorder (PTSD) can result from virtually any type of trauma. Most research is focused in victims who have directly experienced a traumatic event, however, witnessing a traumatic event and not physically experiencing it, can also lead to PTSD. This aspect has received only marginal attention. And, isolation stress can worsen PTSD whether a traumatic event is experienced directly or indirectly. Our laboratory is the first to develop a rat model that depicts effects of witnessing a traumatic event and also compares effect of isolation *vs* bonding on PTSD-like effects in rats. We describe our model as the 'Trauma Witness Model' (TWM).

Methods: Two sets of experiments were conducted. Set I: Sprague Dawley (SD) rats were housed two in a cage, allowed to bond and acclimatize. Then, one of the SD rats was subjected to social defeat stress for 7 consecutive days. During each exposure of social defeat, an SD rat (intruder) was placed into the home cage of an unfamiliar Long-Evans rat (resident). The intruder was defeated assuming supine position. After defeat, a wire mesh enclosure was placed in the cage to prevent physical contact for 5-min. The defeat was observed by the cage mate of the intruder designated as the trauma witnessing (TW) rat, which was present outside the home cage in a clear plexiglass enclosure allowing auditory, sensory and visual stimuli. Two more bouts of social defeat were performed with 5-min separation, to reinforce the visual stress in the TW rat. After social defeat, TW and SD rats were housed together and 24 h later, behavioral experiments examining depression-like, anxiety-like and cognitive functions were conducted. Set II: Similar procedures as above were conducted in this set, except that the TW and SD rats were housed separately after each social defeat exposure.

Results: Our results suggest that witnessing traumatic events leads to severe behavioral and biochemical impairments in rats, which become worse when rats are housed separately. Set I results: A significant decrease in body weight, increased water-intake, increased corticosterone levels, elevated whole body and brain indices of oxidative stress, increased inflammation in the brain, heightened anxiety-like behavior (open-field, elevated-plus maze and light-dark test), increased anhedonia and depression-like behavior (sucrose preference test and forced swim test) as well as learning-memory deficits (Radial arm-water maze test) were observed in TW and SD rats both, as compared to the controls (no resident/trauma). Molecular targets considered critical for anxiety, depression and cognition including Glyoxalse-1, calmodulin-dependent protein kinase (CAMK) IV, cAMP response element-binding protein (CREB) and brain derived neurotrophic factor (BDNF) showed dramatic reductions in specific brain areas including hippocampus and amygdala of TW rats. These levels remained unchanged in the frontal cortex. These effects were comparable to the effects observed in rats that were directly subjected to social defeat trauma and later housed together with cage mate. Set II results: Decrease in body weight, increased water-intake, increased corticosterone levels, elevated whole body and brain indices of oxidative stress, heightened anxiety-like behavior, increased anhedonia and depression-like behavior as well as learning-memory deficits observed in TW and SD rats in set I experiments, were further deteriorated in rats that were housed separately after social defeat exposures. Hippocampus and amygdala exhibited a further decline in the levels of Glyoxalse-1, CAMKIV, CREB and BDNF in these sets of animals, suggesting that perhaps a trajectory involving the above molecules, play an important role in regulation of stress-response.

Conclusions: Data from our rat TWM suggest that witnessing repeated traumatic events are as stressful as experiencing the events first hand, causing severe behavioral and biochemical impairments. Post-trauma conditions such as that of isolation potentially contribute to severity of PTSD-like symptoms in rats. It is of immediate importance to understand the mechanisms by which these effects occur in order to identify suitable treatment strategies. A pathway involving activation of oxidative stress mechanisms, elevation of inflammatory mediators and diminished neuroprotection, all seem to modulate stress response in this model. Finally, our results have direct relevance not only with combat related PTSD but also with increased incidence of day-to-day gun violence related traumatic events, witnessed by people of all ages, in different settings, including our schools, public gatherings and cinema halls.

Keywords: PTSD, trauma, anxiety, oxidative stress, cognition.

Disclosures: S. Salim, Nothing to Disclose; G. Patki, Nothing to Disclose; N. Solanki, Nothing to Disclose; F. Allam, Nothing to Disclose; A. Ansari, Nothing to Disclose.

T10. Identification of Early Risk for Substance Use: fMRI Responses to Cocaine-associated Cues in Juvenile Rats

Steven Lowen, Michael Rohan, Britta S Thompson, Kai Sonntag, Susan L Andersen*

McLean Hospital, Belmont, Massachusetts

Background: Drug-associated cues play a significant role in relapse of drug-seeking behavior. These effects are mediated