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A review on role of neuromodulators in autism spectrum disorder

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Abstract

Autism spectrum disorder (ASD) is a group of complex neurodevelopmental disorders whose diagnosis is exclusively made on a behavioral basis. According to the diagnostic and statistical manual of mental disorders, autism is defined by deficits in two main symptoms (social interaction & communication, and repetitive/restrictive behaviors), which emerge in premature phases of postnatal development. The authors review evidence that ASD is a neurobiological disorder influenced by both genetic and environmental factors affecting the developing brain, and enumerate factors that correlate with ASD risk. Finally, the article describes how clinical evaluation begins with developmental screening.

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Introduction

Autism spectrum disorder (ASD) is a group of complex neurodevelopmental disorders whose diagnosis is exclusively made on a behavioral basis. According to the diagnostic and statistical manual of mental disorders, autism is defined by deficits in two main symptoms (social interaction & communication, and repetitive/restrictive behaviors), which emerge in premature phases of postnatal development. Mutations in a wide variety of autism associated genes can cause neurodevelopmental defects, which subsequently result in social behavior disturbances during early postnatal age and adulthood [1]. Social behavior is characterized by interactions between two or more individuals, normally within the same species, which usually give reciprocal benefits to all individuals involved. Social behaviors related with wide range of brain parts, including areas responsible for motivation, emotions, sensory perception, learning and memory; accordingly, the structure and function of these areas is altered in humans showing altered social behaviors [1]. A different way of classifying social behavior uses the interpersonal circle model of behavior, according to which behavior can be classified along two dimensions, namely agreeable-quarrelsome and dominant-submissive. The dimension of agreeableness and quarrelsomeness bears resemblance to prosocial and antisocial behavior, with prosocial and agreeable behavior typically serving to affiliate with others, whereas antisocial and quarrelsome behavior typically serves to distance the person from others [2]. A variety of neuropsychiatric disorders are characterized by disruptions in social behavior and social cognition, including depression, autism spectrum disorders, bipolar disorder, obsessive-compulsive disorder and schizophrenia. In addition, Deweerdt has reported that withdrawing from social relationships can be a risk factor and an early sign for dementia [3]. Normal social interactions require awareness of multiple factors, including the status of others (such as social dominance or sex) and sensitivity to contextual factors including temporal context and the behavior of conspecifics. The neural circuitry involved in social behavior is commensurately complex and distributed, including limbic, subcortical, and neocortical regions including the prefrontal cortex. The hippocampus has also been implicated in the appropriate sequencing of social behavior. In addition to dependence on intact neural circuitry, social capabilities depend critically upon enough social experience during development [4]. Dendritic cell factor-1 is a protein consisting of 323 amino acids including an N-terminal signal sequence, a mitochondrial targeting sequential motif, a transmembrane region, and a cytoplasmic tail. Suppression of dendritic cell factor-1 promotes differentiation of neural stem cells, implying its effect on brain neural development. Loss of dendritic cell factor-1 in the nervous system induces social interaction deficiency, autism like behavior, and affects social interaction via the dopamine system [5].

Studies of autism have increasingly concentrated on social behavior, as trouble in social functioning is the most fundamental sign of autism. One of the most well define findings in population based studies of autism is the highly skewed male female ratio (M:F) with a two to three times higher prevalence in males. Fundamental differences in social abilities between males and females have also been observed across a wide variety of species including humans. Regarding autism, one of the leading hypotheses of the skewed M:F ratio is the 'Extreme Male Brain' theory proposed by Baron-Cohen, *et al* (2005), which state that the responsibility for autism is strongly affect during fetal development through a pathophysiological alteration of testosterone dependent brain masculinization. Multiple studies have provided increasing support for this hypothesis, including neuropsychological

testing and endocrinological studies [6]. The microbiota gut brain axis has appeared as a new idea in current science explains the potential of gut microbiota to change brain and behavior. Gut microbiota signs in several neurological disorders (autism, multiple sclerosis), metabolic disorders (diabetes, obesity etc) and several aspects of behavior like anxiety, stress, etc. These disorders directly or indirectly influence social behavior [7]. Additionally, social alteration is a central component in the psychopathology of many psychiatric disorders and the dysphoria that accompanies them. Neuroimaging and cognitive neuroscience experiments have found networks that specifically process social information. Molecular and optogenetic studies have identified mark circuit activity encoding representations of social states and dynamics. The specificity and importance of oxytocin for social circuitry and behavior hypothalamic neurons that liberate the neuropeptide oxytocin act selectively to social information, and oxytocin has a central role in the regulation of social behaviors, such as maternal care, closeness, and social memory. Distinct neural circuitry likely regulates these effects. Studies have confirmed the prosocial effects of oxytocin in humans and involved its role in more complex human behaviors, such as trust and empathy [8]. Social practices have strong effects on endocrine factors known to influence adult neurogenesis, recommended several interesting potential connections. Social experience may affect adult neurogenesis by modification in endocrine systems in order to shape the hippocampus so that it produces suitable social behaviour [9].

In particular, trauma experienced from a caregiver during a sensitive window in premature life can produce life-long impairments in threat processing and social behavior across many species. The effects of premature life experience on the brain involve adjustment at nearly every level of analysis, from cellular signaling to behavioral expression. Actually, through the decades, numerous brain areas and nearly every neurotransmitter have been involved in the etiology of psychopathology following early life experiences, including changes in receptors, epigenetics, brain structure, the microbiome, immune system, and homeostasis maintenance. Appearing confirmation recommended brain region can have distinctive function in premature life, such as the important role of locus coeruleus norepinephrine. Improper social behavior is an early symptom of frontotemporal lobar degeneration in both behavioral variant frontotemporal dementia and semantic dementia subtypes. Knowledge of social behavior is necessary for proper social conduct. The superior anterior temporal lobe has been identified as one key neural component for the conceptual knowledge of social behavior, but it is unknown whether this is dissociable from knowledge of the outcomes of social behavior [10]. A common approach about human nature is that people are inherently self-serving. At the same time, humans need ability to inhibited self-serving impulses and to behave in a socially desirable manner for their evolutionary success. Humans and their hominine predator need many physical modifications that other species have but possibly overcame these challenges through living in cooperative groups. Cooperation allow humans to achieve better outcomes (hunting large game, defending themselves against predators, looking after their young) than they could have obtain through individual action. Living in collaborative groups led to norms of socially desirable behavior that requires individuals to inhibit their egotistical impulses and act in another regarding manner instead. An emerging body of research focuses on the role of cognitive control, the ability to guide and balance cognitive processes and behavior flexibly in accordance with one's intentions and goals in socially desirable behaviors, reaching apparently opposite conclusions. Findings recommended that although people experience impulses to capture in egotistical behaviors, they use cognitive control to override impulses, enabling socially desirable ways. Research finds that impairing participants' cognitive control leads to less socially desirable behaviors, such as cheating. Another set of findings revealed that socially desirable behavior is motivated by other regarding impulses rather than cognitive control. Some of this research finds that cognitive control may actually override other regarding impulses. Promoting inherent (rather than controlled) decision making leads to more socially desirable behavior [11].

The medial prefrontal cortex plays a dominant role in generating suitable social responses by supporting behavioral resilience, response inhibition, attention and sentiments. It has been proposed that the medial prefrontal cortex assess and explain information within the context of past experiences and is thus critical for selecting proper behavioral responses within a social environment. For example, injury and pharmacological manipulations of the rodent medial prefrontal cortex modify aggression between males, are need for sex differences in social anxiety, alter social position within a hierarchy and support learned behavioral responses to social defeat, underline the importance of this structure in interpreting and modifying social behaviors in the context of past social experiences. The medial prefrontal cortex projects to several brain regions that are known to affect sociability, including amygdala, nucleus accumbens, hippocampus and brainstem. While several of these predictions have been shown to be critical for medial prefrontal cortex control of nonsocial behaviors and medial prefrontal cortex projections to the raphe nucleus are able to interfere with the stabilizing of adaptation to social defeat, until now the medial prefrontal cortex outputs that directly change social behavior have not been recognize. Projections from medial prefrontal cortex to the dorsal periaqueductal gray, a brainstem motor control area, necessary for defensive responses to social communication, might play a role in the behavioral adaptation to social defeat. This adaptive response, occurring as a result of repeated exposure to threatening members of the same species, is specify by a shift toward a more socially avoidant behavioral strategy, which is probably aimed at inhibiting future harm and facilitating alternative routes to necessary resources. The adaptation to social defeat in animals may have clinical applicability, because mood disorders, including major depression and social anxiety disorder, are assume to involve an extreme form of a versatile coping strategy obtain by social difficulty. Repeated social defeat resulted in increased social avoidance and impaired working memory, both phenotypes that were repair by the antidepressant ketamine. Selective pharmacogenetic retardation of medial prefrontal cortex

projections to periaqueductal gray simulates the effect of social defeat, increasing social avoidance and normalize periaqueductal gray. Social defeat caused depletion in functional connectivity between medial prefrontal cortex and periaqueductal gray, parallel observations made in imaging studies of patients with affective disorders. Cell type specific rabies virus detecting and in vitro channel rhodopsin assisted circuit mapping revealed that layer of medial prefrontal cortex projection neurons directly inhibit excitatory inputs to glutamatergic neurons in periaqueductal gray, and selective inhibition of these target neurons decrease social avoidance. These findings recognize a specific projection by which the prefrontal cortex controls social behavior and indicate how these inputs can be adjusted to adapt social behavior to the environment. Many rodent species, including mice, indicate strong social communities in the wild, and easily quantitated social behaviors in the laboratory.

Role of neuromodulators in autism

Neuromodulation is a defining characteristic of social behavior network function in mammals with estradiol, oxytocin, vasopressin, dopamine, serotonin, glucocorticoids, kisspeptin, gonadotropin releasing hormone, and many more neuromodulators exerting intense effects on behavior through actions in the social behavior network [12]. Of the roughly hundred neuropeptides elucidate in the mammalian brain, most are synthesized and released from the hypothalamus, often with peripheral effects as endocrine hormones. Neuropeptides usually interact with G-protein coupled receptors, through which they act as slow neurotransmitters or neuromodulators [13]. Neuropeptides act rapidly on multiple spatial scales and regulate the translation of sensory information into behavior through these actions.

1. Oxytocin and vasopressin

Two of the well studied neuromodulators affecting social behavior network function are the evolutionarily preserved neurohypophysial hormones oxytocin and vasopressin, first isolated in 1953. Oxytocin and vasopressin differ in only two amino acids, but have intensely different effects on behavior and circuit function. These small peptides have now been related with a huge range of behavioral, physiological and neuroendocrine functions. Oxytocin rapidly activates medial amygdala neurons, promotes social behavior, and decrease fear induced behaviors. Recent study revealed that social rewards mediated by oxytocin required the oxytocin dependent improvement of long term depression at serotonergic synapses in the nucleus accumbens. Yet, we still know relatively little concerning the wide actions that vasopressin or oxytocin apply on the moment to moment function of social circuits [14]. More relevant to social neuroscience, oxytocin and vasopressin expressing neurons in the hypothalamus project centrally, and oxytocin, vasopressin receptors are found in the brain. Vasopressin was reported to have central effects on memory and aggression, among many other behaviors. Oxytocin and vasopressin can also effect early processing of social perception. Oxytocin increases trust, empathy, eye contact, face memory, generosity and reduces anxiety. Oxytocin lower the amygdala activation following allowing stimuli, the study indicate that the oxytocin effect on amygdala activation could be more obvious in the response to social threats versus nonsocial threats. In fact, oxytocin appears to lowers the amygdala response to emotional expression irrespective of valence [15]. Homologues of the mammalian oxytocin and vasopressin neuropeptides and their respective target receptors modulate social and reproductive behaviors across bilaterian animals including social behavior, social cognition, and psychiatric phenotypes such as autism spectrum disorder in humans [16].

2. Serotonin

Serotonin is a key neurotransmitter that appeared early in development and affected a variety of social approach across species, from humans to primates, rodents and flies. Enhanced serotonin levels in the brain have been connected to social behaviors such as integration and cooperation. Study has shown social behaviors such as aggression and impatient, as well as certain disorders are associated to disturbances in serotonergic functioning. Serotonin malformation has been found to be related with antisocial, impulsive, and violent criminal behaviors. Given this related between serotonin function and social behavior, there is the possibility that altering serotonin could lead to positive changes in social behavior [17]. The serotonin receptor 5-Ht2cR, encoded by the 5Htr2c gene, is a G-protein coupled receptor and modulates cellular excitability. Pharmacological studies in animal models have revealed roles for serotonin receptor in communication and social interaction. Activation of serotonin receptor by meta-chlorophenylpiperazine, a nonselective agonist, reduces social interaction in rodents. Conversely, administration of the selective serotonin receptor antagonist SB242084 in rats enhances social interaction and recovers social impairment caused by stress or meta-chlorophenylpiperazine. Deregulated action of serotonin receptor has been involved in autism spectrum disorder, which features impaired in social interaction and communication. There is proof of a physical interaction between serotonin receptor and Pten, a negative regulator of the PI3-kinase pathway and a risk factor for autism. However, it is not known how chronic alteration in serotonin receptor activity during development affects social behavior [1, 2].

3. Gamma-aminobutyric acid

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system and gamma aminobutyric acid releasing cells play the role of intended neuronal excitation, inhibiting brain hyper excitability. Huge disruption of GABAergic function results in serious disease such as epilepsy, and is believed to occur in autism as well. The maintaining of a correct inhibitory to excitatory stability is necessary to encourage development and plasticity, as clearly described for sensory region of the brain. Interestingly, enhancement in perceptive, noticeable and sensational tasks has been reported in humans influenced by social behavior disturbances. Loss of GABAergic function, with resultant neuronal hyper excitability, slightly improves emotional skills, but dramatically impair sensorial processing, triggering a hyper arousal condition during the first step of internal elaboration [4, 6].

4. Dopamine

Dopamine is a neurotransmitter implicated in various neurochemical and neurohormonal activities that influence and alter animal behaviour and cognition. Dopamine alters a variety of brain functions, and their altered levels have been involved in the pathophysiology of affective disorders. Dopamine is related with motivation, reward, and hedonic states; therefore, enhanced dopamine levels could possibly treat depression. It has been proven that dopamine agonists can improve depressive symptoms. Dopamine receptor D_1 mediates the effects of antidepressant drugs in the forced swim test whereas dopamine receptor D_2 antagonists blocked the effect of antidepressant drugs in the forced swim test. Although dopamine and dopaminergic receptors are implicated in social interaction, the underlying neural mechanisms are arguable [2, 10].

5. Cannabinoid

The brain distribution with molecular components of the endocannabinoid system is stable with a role in social behavior. CB1 cannabinoid receptors are highly expressed in related areas of the frontal cortex and in subcortical structures that sustain human social emotional functioning. They are also present throughout areas involved in the beneficial properties of natural and drug associated stimuli, including the central and basolateral amygdala, prefrontal cortex, hippocampus, dorsolateral striatum, ventral tegmental region, and to a lesser extent, the nucleus accumbens. These areas are considered key parts of the social brain. The regional distribution of the enzymes implicated in the generation and degradation of endocannabinoid transmitters is similar to the picture of CB1 receptors [7].

6. Acetylcholine

The cholinergic system is one such possible constituent. In the central nervous system, acetylcholine is necessary in evaluating the beneficial or threatening valence of stimuli and changes in environment, and responding accordingly. Therefore, it has a role in controlling behaviors applicable to autism including attention, cognitive flexibility, social interactions and stereotypical behaviors. Neurons in a basal forebrain cholinergic nucleus of autism patients are abnormal in size, number, and structure. Reduced concentrations of choline, a precursor of acetylcholine and nicotinic cholinergic receptor agonist, and low levels of cytosolic choline were associated with the severity of autism [8, 11].

ANIMAL MODELS

Over the last decade, a considerable number of rodent models of autism have been produced and revealed face validity by important behavioral traits relevant to autism. Well characterized social and communication evaluation pattern and experiment for the presence of repetitive behaviors exist for rodent models of autism. Animal models are discussed in three groups; (i) models with acquired behaviors resulting from environmental effect, (ii) models expressing a human genetic mutation related with autism and (iii) naturally occurring rodent strains that revealed behavioral endophenotypes relevant to autism [6, 9].

Environmental models

Autism spectrum disorder like features displayed by environmental rodent models are generally obtain in response to an clear insult or developmental challenge, such as exposure to toxins resulting in altered neurological development.

1. Valproate model

During pregnancy, maternal exposure to the first generation antiepileptic drug valproate has been shown to significantly enhance the risk of autism in children. Valproate is a short-chain fatty acid and is thought to decrease neuronal excitability primarily by increasing concentrations of the inhibitory neurotransmitter gamma aminobutyric acid and altering voltage gated sodium channels. In both mice and rats, administration to valproate during gestation via intraperitoneal injection or orally with food produces impaired in social interaction and repetitive behaviors. These animals also show decrease sensitivity to pain and olfactory cues, enhanced touch sensitivity and diminished listening pre-pulse inhibition, a test commonly used to index abnormalities in sensorimotor gating. Valproate introduced adult rats show increased levels of anxiety like behaviors and a decreased threshold for electroshock and pentylenetetrazole induced seizures. These rats also show altered circadian rhythms characterized by frequent movement during the sleep phase [11, 18].

2. Propionic acid model

The gut microbiota has been suggested to play a role in the etiology of autism. Potential mechanisms contributing to autism phenotypes are unknown, however excessive toxin producing bacteria have been recognized in patients with autism and enhanced levels of short-chain fatty acids (such as propionic acid) produced by enteric bacteria have been studied in rats. In rodent models, administration of the endogenous short-chain fatty acids butyric acid, sodium acetate and propionic acid directly into the cerebral ventricles produces endophenotypes related to autism. Acute intracerebral ventricular infusion of propionic acid in rats reduces sociability and learning and also produces sensorimotor impairments. This model also results in reduced cognitive flexibility during reversal learning. Furthermore, repeated intraventricular propionic acid infusion leads to increased susceptibility to kindling induced seizures and stereotypic behaviour [13].

Genetic models

Many gene mutations related with autism code for proteins implicated in the formation and maintenance of synapses. Monogenic mouse models shows mutations in four genes affecting synaptic function; the neuroligin-3^{R451C} mice two models expressing specific mutations in the Shank3B/ProSAP2 gene [Shank3B knockout mice and $Shank3B^{e4–9}$ partial knockout mice, as well as two SHANK2 knockout models and the contactin associated protein-like 2/Neurexin IV (CNTNAP2/NRXN4) knockout mouse model. Electrophysiological studies in these mice report altered glutamatergic and GABAergic synaptic function. Each of these models also expresses strong autism behavioral endophenotypes suggesting a role for these genes in shaping core behaviors relevant to autism diagnosis. However, it is not

well established whether these animal models replicate comorbid traits observed in patients [1].

Brain derived neurotrophic factor

Brain derived neurotrophic factor (BDNF) is a secretory protein and a member of the neurotrophic factor family, which is widely expressed in the brain and periphery. BDNF has been prefer as a possible gene for autism susceptibility and plays a key role in the growth and differentiation of new neurons and synapses, as well as in the survival of existing neurons. Children with autism were described to possess higher BDNF levels in the blood, compared with typically developing individuals. Furthermore, autistic adults have been described to have enhanced BDNF levels in the basal forebrain. These results suggest that over expression of BDNF at various developmental time points could be related with autism and may be a repressed mechanism of brain overgrowth in autistic patients. But, the role of BDNF in autism etiology remains indefinite, as new work revealed completely opposite results, results lowers serum BDNF levels in autism patients. These negative outcomes make BDNF a variable and possible undependable biomarker for autism; yet, it is clear that optimal levels of BDNF are necessary for brain development and maintenance of normal brain function [8].

1. Neuroligin-3^{R451C} mice

Neuroligins are adhesion molecules which combine with a range of post-synaptic scaffolding proteins including Shank3 and contactin associated protein-like 2 and bind to members of the presynaptic neurexin family across the synaptic cleft. Mutations in the neuroligin family of post-synaptic adhesion molecules were involved in autism after a voluntary point mutation in the gene encoding neuroligin-3 was recognized in two brothers with autism; one with comorbid epilepsy. Mice expressing the neuroligin-3^{R451C} mutation show a fine depletion in pup distress calls and decrease listening alarm. Under some conditions and on some genetic backgrounds, neuroligin-3^{R451C} mice also show impaired social interaction. Delays in meeting developmental milestones, which may appear as motor deficits early in development, have also been notice in these mice. However, adult neuroligin-3^{R451C} mice showed better motor coordination in the accelerating rotarod test compared with wild type littermates [1].

2. 7-dehydrocholesterol reductase altered mice

7-dehydrocholesterol reductase (DHCR7) is a commonly expressed catalytic enzyme that converts 7-dehydrocholesterol to cholesterol. Alteration in DHCR7 function is the main reason of Smith Lemli Optiz syndrome, which is often comorbid with autism. Optiz syndrome patients have unusual behavioral phenotypes including increased hyperactivity, irritability, aggression, insomnia, self-injurious behavior, repetitive and ritualistic behaviors, and impaired communication. Interestingly, low cholesterol levels have been observed in children with idiopathic autism. Similar to BDNF homozygous knockouts, DHCR7 null (-/-) mice have high lethality rates at birth; therefore, DHCR7+/- or DHCR7 mutant mice are used as animal models. DHCR7+/- mice show low exploratory activity both in the social preference and open field tests. DHCR7 mutant mice show increased ventricular size and malformation in the hippocampus and serotonergic neurons. The DHCR7-heterozygous mice display increased response to treatment with a serotonin-2A agonist, suggesting the involvement of the serotonergic system in the phenotypes observed in the model [8].

3. Shank3 mice

The Shank3 (SH3 and multiple ankyrin repeat domains) gene family also known as proline rich synapse associated proteins contains three members; Shank1-3 that code for post-synaptic scaffolding proteins implicated in the entry of several receptors and proteins (including the neuroligins and neurexins) to the excitatory post-synaptic membrane. Rare microdeletions within the 22q13 locus (containing Shank3) are related with intellectual disability, speech delay, and autism. Mutations in Shank2 are also related with autism. Two different genetic models in which Shank3 is altered; Shank3B$^{-/-}$ and Shank3^{e4-9} in addition to two newly reported Shank2 knockout models revealed core and comorbid traits relevant to autism. A third model in which one full length copy of Shank3 is deleted shows core autism endophenotypes; however the expression of secondary/comorbid properties define here has not been investigated in these mice. Shank3B$^{-/-}$ mice lacking the Shank3α and β isoforms show increased repetitive behavior (self-injurious grooming) and reduced interaction with a unknown mouse as well as infrequent handling induced seizures. Shank3^{e4-9} mice (in which exons 4-9 are deleted) show core autism like deficits including social impairments, repetitive behaviors, and impaired communication (less complex vocalization patterns), with learning deficits and mild motor abnormalities also evident. In addition to a role as a structural protein in the central nervous system, Shank3 is present at enteric nervous system synapses. The enteric nervous system controls gastrointestinal motility and mucous secretion and hence gene mutations leading to changes in synaptic function (including many autism candidate genes) may also influence gastrointestinal function. The Shank3 mouse models of autism are hence excellent candidates for investigating effects of autism related gene mutations on gastrointestinal motility. Shank2 knockout mice revealed abnormal vocal and social behaviors, and increased grooming behaviors. Hyperactivity (repetitive jumping) and anxiety like behaviors have also been reported in these mice detected no change in aggressive behaviors in Shank2 knockout mice using a resident intruder test. Despite this negative result, a high level of aggression between Shank2 knockout males was observed in home cages [1].

4. Fragile X mental retardation-1

Fragile X mental retardation 1 (FMR1) gene encodes for fragile X mental retardation protein (FMRP). FMRP is an RNA binding protein that is commonly expressed in brain, testes, and ovaries. FMRP takes part in local protein synthesis regulation in dendrites, as well as mRNA transport from nucleus to the cytoplasm. FMRP plays an essential role in synapse development, which is essential for proper neurotransmission, learning and memory, and synaptic plasticity. Mutations in FMR1 take the form of expanded CGG trinucleotide repeats in the 5' gene untranslated region, this stops the production of FMRP and leads to a developmental condition called fragile X syndrome which is characterized by intellectual disabilities,

developmental delays, congenital abnormalities, seizures and autistic like symptoms. Fragile X syndrome patients were also diagnosed with autism [8].

5. CNTNAP2 mice

Genetic ablation of the contactin associated protein-like 2 (CNTNAP2) gene, a member of the neurexin transmembrane protein superfamily (also known as CASPR2 and neurexin IV), results in autism like deficits in social interaction and stereotypic behaviors in mice. In addition, CNTNAP2 knockout mice show hyperactivity, impaired nest building, and frequent handling induced seizures after six months of age. The CNTNAP2 gene has been associated with autism and a recessive form of epilepsy. These mice show sensory endophenotypes including hyper reactivity to thermal sensory stimuli and better performance in the buried food test, an assay for olfactory function. CNTNAP2 knockout mice also exhibited slightly improved motor coordination on the rotarod contrast to wild type littermates. Possibly, the atypical antipsychotic risperidone (prescribed to treat aggression and irritability in some cases of autism) abrogate nest building deficits as well as locomotor hyperactivity in these, revealing predictive validity in this model [1].

Phenotype Models

Interplay between genomic and non genomic influences (maternal effects) is almost certainly implicated in the symptom heterogeneity related with autism. There are presently some rodent models developed via breeding processes alone that show significant endophenotypes relevant to the diagnostic criteria and comorbid traits related with autism. These animal models include the FAST/SLOW rats and the C58/J, BALB/c, BtBR T + tf/J (BTBR), and epileptic like mice.

1. FAST/SLOW rats and EL mice

The FAST and SLOW rat strains were obtain from parent populations of Long Evans Hooded and Wistar rats using selective breeding processes based on relative seizure susceptibility in the amygdala kindling model. This procedure ultimately creates a seizure susceptible (FAST) and seizure resistant (SLOW) strain. FAST rats have since show highly seizure susceptibility in both the kindling model and in chemoconvulsant (e.g., pilocarpine, kainate) seizure induction models. Epileptic like mice, like FAST rats, were also produce via selective breeding based on relative seizure susceptibility and originated from the non epileptic DDY mouse strain. Epileptic like mice typically exhibit handling induced seizures by postnatal day 50–60. Remarkably, the breeding processes used to produce heightened seizure sensitivity in both colonies simultaneously produced strong, comorbid autism like traits. Both FAST rats and epileptic like mice exhibit significant social impairment and repetitive behaviors (overgrooming, self-injurious behavior, and myoclonic jumping) alongside delays in social, physical, and visuomotor development, learning deficits, impulsivity, and hyperactivity in different testing models. FAST rats are also more aggressive than their comparison SLOW strain and show reduced listening alarm but enhanced fear conditioning. Thus, FAST rats and epileptic like mice offer a similar endophenotypic profile relevant to fundamental and comorbid symptoms observed in autism [1].

2. C58/J mice

C58/J mice naturally showed autism like symptoms including poor sociability, relative learning deficits, hyperactivity, and stereotypic behaviors (jumping and flipping). Interestingly, C58/J mice also indicate a reduced threshold for pentylenetetrazole induced seizures. However, as compared to the autism like developmental delays detect in FAST and epileptic like animals, C58/J mice meet developmental milestones earlier than their comparison strain [1].

3. BALB/c and BTBR mice

The BALB/c and BTBR mouse strains shows core autism symptoms in the form of impaired social interaction and repetitive behaviors (overgrooming and/or excessive marble burying). BTBR mice also demonstrate increased social anxiety like behavior although anxiety responses to novel situations are irregular. BTBR mice are less reactive to thermal stimuli than the C57Bl/6J standard strain, suggesting subtle sensory changes exist in this model. Several BALB/c substrains displaying distinct behavioral phenotypes offer particular strengths for comorbidity investigation. BALB/cJ mice show altered gastrointestinal function and are highly aggressive while the epilepsy susceptible BALB/c substrain is sensitive to audiogenic seizures. BTBR and BALB models have a high incidence of corpus callosal agenesis and severely reduced hippocampal commissural volumes, which may be relevant to reports of reduced corpus callosal volumes in autism patients [1].

Conclusion

ASD is a neurodevelopmental disorder characterized by deficits in social communication and the presence of restricted interests and repetitive behaviors. ASD is a neurobiological disorder influenced by both genetic and environmental factors affecting the developing brain. As social neuroscience go forward, it will become ever more important to apply methods that allow assumption about cause and effect. The combination of pharmacological manipulations with neuroimaging will facilitate the identification of the brain networks that are causally involved in generating social cognition and behavior.

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