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7

Nicotinic Acetylcholine Receptor Alterations in Autism Spectrum Disorders – Biomarkers and Therapeutic Targets

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1. Introduction

Autism Spectrum Disorders (ASD) are a set of complex neurodevelopmental disorders defined behaviorally by impaired social interaction, delayed and disordered language, repetitive or stereotypic behavior and a restricted range of interest (Fombonne, 1999). ASD affect nearly 1 in 110 children, and disproportionally affect four times as many boys as girls. Comorbid symptoms often include seizures, sleep problems, gastrointestinal disorders, and metabolic deregulation (Coury, 2010). As such, ASD are an enormous challenge for parents, medical professionals, and educators. Their treatments put a significant financial strain on healthcare systems worldwide. There is no pharmacotherapy proven effective for treating the core deficits in ASD. There is also a paucity of biomarkers for autism. Both genetic and environmental factors are thought to contribute to autism susceptibility (Courchesne, 2007; Geschwind, 2009; Südhof, 2008; Ramocki & Zoghbi, 2008), but because only some of the genetic factors have been identified unequivocally thus far (Cook & Scherer, 2008; Levitt & Campbell, 2009), finding effective treatments that target the underlying causes of ASD remains a major challenge.

Identifying endophenotypes and biomarkers for complex and heterogeneous disorders such as ASD are important not only to elucidate their etiologies, but also to identify suitable biochemical molecules and pathways to target the treatment of core deficits. In this review, we present a rationale that neuronal nicotinic acetylcholine receptor (nAChR) alterations are biomarkers for ASD and that specific nAChRs subtypes are likely to be useful therapeutic targets for the treatment of core deficits. This rationale is based on the synthesis of emerging evidence from multiple types of studies, including our own, using postmortem, genetic, functional, and molecular neurobiological methodologies from two disparate areas of research – autism spectrum disorders and nicotine dependence.

2. Neuronal nicotinic acetylcholine receptors

Neuronal nAChRs are a family of ion channels that are permeable to both monovalent (Na^+ and K^+) and divalent (Ca^{++}) cations and are formed by assembly of different combinations of subunits termed α2 to α10 and β2 to β4. These channels are heteropentamers with the exception of the α7 nAChR, which is usually a homopentamer (Lindstrom, 1996; Lindstrom, 1997; Sargent, 1993). In neurons, nAChRs regulate the release of many different neurotransmitters including acetylcholine, dopamine, γ-aminobutyric acid (GABA), glutamate, and serotonin at presynaptic sites (McGehee & Role, 1996) and mediate fast synaptic transmission at postsynaptic sites (Zhang et al., 1996; Frazier et al., 1998a; Frazier et al., 1998b). These functions have a broad range of physiological effects on reward, analgesia, anxiety, affect, locomotion, attention, mood, learning, memory, and executive function (Miwa et al., 2011). nAChRs can also modulate neurite growth (Pugh & Berg, 1994; Lipton et al., 1988) and cell survival (Pugh & Margiotto, 2000; Messi et al., 1997; Kihara et al., 1997; 1998; 2001). nAChRs have been intensely studied for many decades not only to understand their normal physiological roles, but more importantly to elucidate their pathophysiological role in mediating addiction to nicotine in tobacco, because tobacco use among smokers, in particular, results in greater than 400,000 deaths per year in the U.S. alone. In addition to their role in nicotine addiction, nAChR dysfunctions are also implicated in other disorders, including Alzheimer's disease, Parkinson's disease, schizophrenia, attention deficit-hyperactivity disorder, anxiety disorders, Tourette's syndrome, and depression (Newhouse & Kelton, 2000; Newhouse et al., 2004; Mineur & Picciotto, 2010).

3. Alterations of nAChRs in ASD

3.1 Changes in α4β2 nAChR expression

Examination of postmortem brains of individuals with ASD has identified major nAChR abnormalities in multiple postmortem studies. In the first such study to be undertaken, postmortem tissue from 7 adults with a mean age of 24 years was examined. High-affinity ^{3}[H]epibatidine binding was reported to be significantly reduced in the frontal and parietal cortex of these individuals with ASD compared to age-matched controls. Furthermore, immunohistochemical analyses showed that the loss of ^{3}[H]epibatidine correlated with reduced expression of the α4 and β2 nAChR subunits. Notably, the mRNA for these two nAChR subunits was not significantly decreased, suggesting that the reduction in nAChR subunit levels resulted from an impaired posttranslational mechanism. Also, ^{3}[H]pirenzepine binding to M1 and M2 muscarinic AChRs (mAChRs) was not significantly altered, suggesting that the loss of nAChR expression resulted from deregulation of a posttranslational mechanism that specifically affected nAChRs, but not mAChRs (Perry et al., 2001). In a subsequent study, postmortem tissue from 8 adults with a mean age of 24 years was examined. Again, high-affinity [^{3}H]epibatidine binding was reported to be significantly reduced by greater than 50% in the cerebellar cortex of individuals with ASD. High-resolution analyses of the autoradiographic data indicated that the loss of ^{3}[H]epibatidine binding occurred in the granule cell layer, the Purkinje layer, and the molecular cell layer of the cerebellum of individuals with ASD compared to age-matched controls. Significant reduction in the expression of the α4 nAChR subunit, but not its mRNA (Lee et al., 2002), was also observed and is consistent with the notion that α4β2 nAChR loss results from an impaired posttranslational mechanism regulating it expression. In a third

study, immunohistochemical analysis of postmortem brains from 3 adults with ASD of mean age 29 years surprisingly showed no changes in the expression of the α4 nAChR subunit in the thalamus compared to age-matched controls. However, reduction of the β2 nAChR subunit was observed in the paraventricular nucleus and nucleus reuniens of the thalamus (Martin-Ruiz et al., 2004).

3.2 Changes in α7 nAChR expression

In contrast to the loss of ^{3}[H]epibatidine binding and decreased expression of the α4 and β2 nAChR subunits, no significant change in the binding of ^{125}I-α-bungarotoxin to the α7 nAChR or immunohistological detection of the α7 nAChR (Perry et al., 2001) was reported in the frontal and parietal cortex. In the cerebellar cortex, however, binding of α-bungarotoxin to the α7 nAChR and immunohistological detection of the α7 nAChR did show a significant increase in the expression of the α7 nAChR in the granule cell layer, but not in the Purkinje cells or the molecular cell layer. Interestingly, similar to the β2 nAChR subunit, reduction of the α7 nAChR subunit was also observed in the paraventricular nucleus and nucleus reuniens of the thalamus. Thus, alterations in the expression of both the α4β2 nAChR and the α7 nAChR in individuals with ASD appears to show regional specificity (Perry et al., 2001; Lee et al., 2002; Martin-Ruiz et al., 2004), suggesting that these changes are compensatory and result from altered homeostasis of neural networks, rather than the direct effect of a single molecule in a particular molecular pathway.

Two recent studies on rare genomic microdeletions and copy-number variations (CNVs) revealed a possible involvement of the CHRNA7 gene in some cases of autism. The first study investigated segmental duplications at breakpoints (BP4–BP5) of chromosome 15q13.2q13.3 from 1441 individuals with autism from 751 families in the Autism Genetic Resource Exchange (AGRE) repository (Miller et al, 2009). This genomic sequence spans over 1.5 Mb and includes CHRNA7. From this cohort 10 patients were identified with genomic imbalance at chromosome 15q13.2q13.3, including five with BP4–BP5 microdeletions. Among the 1420 parents and 132 unaffected/unknown siblings no cases of BP4–BP5 microdeletion were found. The second study on genomic CNVs explored the genetic contribution to ASD in a large cohort of families (Simons Simplex Collection consisting of 915 families) with a single autistic child and at least one unaffected sibling (Levy et al., 2011). The contribution of the transmission of ''ultrarare'' variants to ASD, in particular inherited genomic duplications was also estimated. A transmitted duplication within the CHRNA7 gene was observed in 8 autistic children and 3 unaffected siblings within 6 families. A further network-based analysis of genetic associations (NETBAG) of that dataset strengthened the involvement of CHRNA7 as one of the genes affected by rare de novo CNVs in autism (Gilman et al., 2011).

4. nAChRs modulate multiple behaviors deficient in ASD

ASD is defined by three behavioral deficits, impaired social interactions, repetitive behaviors, and delayed language. Multiple studies using animal models implicate a functional role for nAChRs in some of these behavioral deficits in ASD. β2-containing nAChRs regulate executive and social behaviors in studies using β2 nAChR subunit knockout mice (Granon et al., 2003). Knockout β2 nAChR mice show a decrease in slow exploratory behavior - a measure of cognitive function during which animals slowly and

precisely explore their environment, a lack of sensitization to novel stimuli, and abnormal social behavior during aggressive confrontations with other mice (Granon et al., 2003). Recovery of the slow exploratory behavior was observed by injecting a lentiviral vector expressing the β2 nAChR subunit into the ventral tegmental area (VTA) in the knockout mice (Maskos et al., 2005). Re-expressing the β2 nAChR subunit in the prefrontal cortex also improves social abnormalities in this knockout mouse. Increased social interaction and decreased novel exploration in a social interaction paradigm with concurrent motivation was ameliorated after stereotaxically injecting the β2 nAChR subunit into the prelimbic area of the prefrontal cortex (PFC) (Avale et al., 2011).

As previously mentioned, nAChR dysfunction is also implicated in several other neurological disorders with repetitive behavior. We suggest here that similarities in behaviors across those neurological conditions, as well as high prevalence of simultaneity suggest a possible shared underlying mechanism. Moreover, there has been a recent push to redefine repetitive behavior in these neuropsychiatric disorders and instead characterize stereotypies into disorder-related endophenotypes rather than separate disorder-specific symptoms (Kas et al., 2007, Langen et al., 2011). Tourette's syndrome (TS), obsessive compulsive disorder (OCD), and attention deficit hyperactivity disorder (ADHD), all involve disordered cortical-basal ganglia circuitry and all can be successfully treated with drugs acting on nAChRs. The basal ganglia and orbitofrontal cortex, both regions highly innervated by nicotinic acetylcholine receptor rich interneurons are hyperactive during PET/SPECT studies of OCD (Baxter et al., 1988) and hypoactive in studies of ADHD (Zametkin et al., 1990) and TS (Braun et al., 1995). The orbitofrontal cortex controls inhibition and disinhibition of behavior, and lesions in this area are sufficient to cause impulsive and inappropriate behavior. Nicotine or an analog alone has demonstrated potential to treat repetitive behaviors in these disorders. A transdermal nicotine patch, administered as therapy for TS, decreases the severity and frequency of tics, a compulsory symptom of TS (Sanberg, 1997). Nicotine gum administered to OCD patients previously resistant to other treatment clinically improved behavior (Carlsson, 2001; Pasquini et al., 2005). Interestingly, clomipramine, an SSRI commonly prescribed for the treatment of OCD, also acts on nAChRs (Lopez-Valdes, 2002). Lastly, (-)-Nicotine and ABT-418, an α4β2 nAChR agonist (Potter et al., 1999), both successfully treat adults with ADHD (Levin and Simon, 1998; Wilens et al., 1999). It is interesting to note that hyperactivity, tics, and obsessive compulsive disorder are all common comorbid disorders seen in patients with ASD with approximately 59% of ASD patients having impulsivity problems, 8-10% having tics, and 37% having OCD (Levy et al., 2009). Although it is clear that similar neurocircuitry is involved in several disorders with repetitive behavior, further research is needed to determine whether the underlying mechanisms causing this dysfunction overlap in TS, OCD, ADHD, and in ASD.

nAChRs also are involved in several other non-core, but frequently occurring symptoms in ASD. The most common comorbid disorders and symptoms associated with ASD are psychiatric (e.g., depression and anxiety), neurological (e.g., epilepsy), sleep, and sensory (e.g., tactile) disorders. Epilepsy occurs in 5-49% of people with autism (Levy et al., 2009). Genetic abnormalities in CHRN4A and CHRNB2, encoding the α and β nAChR subunits respectively, are sufficient to cause autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) (De Fusco, 2000; Bertrand, 2002; Steinlein, 2002; Hoda, 2009), however ADNFLE is not associated with ASD. 52-73% of patients with ASD experience sleep disruption and 43-84% experience anxiety disorders. Knocking out the α4 nAChR subunit increases anxiety

in mice (Ross et al., 2000) and the β2 nAChR knockout animal shows abnormal sleep pattern (Lena et al., 2004). These studies demonstrate that behaviors regulated by nAChRs are disparate and commonly aberrant in ASD and suggest the potential for nAChR-acting drugs in the treatment of ASD.

Lastly, there is accumulating evidence that the immune system is disrupted in individuals with ASD (Careaga et al., 2010). Elevated levels of chemokines have been detected in the brains and cerebrospinal fluid (Chez et al., 2007; Wills et al., 2009) as well as the plasma (Ashwood et al., 2011a) of individuals with ASD, and this elevation correlated with more impaired behavior (Ashwood et al., 2011b). Furthermore, postmortem studies of individuals with autism also detected presence of activated neuroglial cells in their brain (Vargas et al., 2005). In a recent study, activated microglia were detected in the dorsolateral PFC in 5 out of 13 samples, 2 of which were under the ages of 6 years (Morgan et al., 2010). These results suggest that inflammation of the central nervous system, at least in some individuals, may contribute to the neuropathology of ASD. Thus, suppression of neuroinflammation by targeting α7 nAChRs in ASD may be potentially beneficial.

5. Neurexin and neuroligin deficits in ASD

The neurexins are cell adhesion molecules encoded by three genes corresponding to neurexins 1, 2 and 3 (Missler & Südhof, 1998; Lise & El-Husseini, 2006). As a result of transcriptional initiation from two different promoters, each neurexin gene encodes a longer α-neurexin protein and a shorter β-neurexin protein. The proteins are identical from their intracellular C-termini through their transmembrane domains, glycosylation-rich domains and the sixth LNS domain of α-neurexin, which corresponds to the only LNS domain in β-neurexin. They have divergent N-terminal extracellular domains, which allow for interactions with multiple proteins. Additionally, alternative splicing at multiple splice sites within each gene can give rise to more than one thousand different isoforms, which differ only in their extracellular domains. Neurexins recruit N- and P/Q-type calcium channels to active zones of presynaptic terminals through scaffolding proteins, including calmodulin-associated serine/threonine kinase (CASK) (Hata et al., 1996; Missler et al., 2003; Zhang et al., 2005). α-neurexins were reported to specifically induce GABAergic postsynaptic differentiation (Kang et al., 2008). The enormous structural diversity of the neurexins suggests that they are involved in a multitude of physiological functions yet to be elucidated.

Results from a linkage and copy number variation analysis conducted by the Autism Genome Project Consortium (Szatmari et al., 2007) show that neurexin-1 dysfunction is associated with ASD. This conclusion has been corroborated in multiple linkage analysis studies since (Kim et al., 2008; Marshall et al., 2008) and in analysis of structural variants in the α- and β-neurexin genes (Zahir et al., 2008; Feng et al., 2006; Yan et al., 2008; Gai et al., 2011; Gauthier et al., 2011). Neurexin knock-out animals have provided insights into the functions of the neurexin family. Neurexin 1/2/3α- triple knock-out animals die perinatally and have reduced spontaneous and evoked neurotransmission at glutamatergic and GABAergic synapses, demonstrating that α-neurexins are necessary for neurotransmitter release at synapses (Missler et al., 2003). Additionally, mice lacking neurexins have impaired neuroendocrine secretion (Dudanova et al., 2006), which may mirror some children with autism that exhibit dysfunction of the hypothalamic-pituitary-adrenocortical system,

possibly due to altered neuroendocrine regulation (Corbett et al., 2006). Similar to the neurexin triple knockout animals, mice lacking neurexin1/2α or neurexin2/3α die within 1 month after birth and have reduced neurotransmission. Analyses of brain morphology in α-neurexin knockouts revealed no major impairments in synapse formation, but minor reductions in dendrite branch length and spine numbers were detected, suggesting they are important in synapse maturation more so than formation (Dudanova et al., 2007). None of the single α-neurexin knock-out animals have dramatic phenotypes, with the neurexin-2α knock-out animals showing the least severe phenotype (Craig & Kang, 2007). In the absence of neurexin-1α, miniature excitatory postsynaptic currents were reduced in recordings from hippocampal slices. Behaviorally, the neurexin-1α–deficient mice were identical to wild-type mice in multiple social interactions, but displayed decreased grooming behavior, impaired nest building, decreased pre-pulse inhibition, and improved motor learning in behavioral studies (Etherton et al., 2009). While the neurexin-1α–deficient mice display behavioral phenotypes similar to what is seen in autism they are not sufficient to explain ASD yet they still provide a useful but limited model of ASD. The β-neurexin and combined α- and β-neurexin knockout animals have not yet been fully evaluated.

The neuroligins are encoded by five differentially spliced genes that encode multiple neuroligin isoforms (Zhang et al., 2005; Boucard et al., 2005). In complementary roles, neuroligins, the postsynaptic binding partners of neurexins, recruit N-methyl-D-aspartate (NMDA) receptors and $GABA_A$ receptors through their interactions with scaffolding proteins such as post-synaptic density 95 (PSD-95) and gephyrin, respectively (Graf et al., 2004; Nam & Chen, 2005; Chih et al., 2006; Poulopoulos et al., 2009). Thus, bi-directional interactions between neurexins and neuroligins appear to serve a critical function in the assembly and maturation of both glutamatergic and GABAergic synapses through recruitment of the requisite presynaptic and postsynaptic components of neurons (Dean & Dreshbach, 2006; Craig & Kang, 2007; Sudhof, 2008).

Neuroligins are strongly implicated in ASD. Chromosomal rearrangements and copy number variations in neuroligin-1 are linked to autism (Konstantareas & Homatidis, 1999; Ylisaukko-oja et al., 2005; Glessner et al., 2009). There is also evidence that mutations in neuroligin-3 and neuroligin-4 are found in patients with ASD (Laumonnier et al., 2004; Jamain et al., 2003). In addition mouse models support a role for neuroligins in ASD. Neuroligin-1 knock-out mice are viable and fertile, but also have synaptic dysfunctions (Chubykin et al., 2007). At the molecular level, the NMDA/AMPA ratio at corticostriatal synapses is reduced, which is associated with repetitive grooming that may mirror some of the repetitive behaviors seen in autistic patients (Blundell et al., 2010). In contrast to neuroligin-1-deficient mice, which show impaired NMDA receptor signaling, neuroligin-2 knock-out animals have deficits in inhibitory synaptic transmission (Chubykin et al., 2007). Behaviorally, neuroligin-2 knock-out mice exhibit increased anxiety, but normal social interactions (Blundell et al., 2009), similar to the neurexin-1α-deficient mice. Mutations in neuroligin-3 and neuroligin-4 lead to intracellular retention of the mutant proteins (Chih et al., 2004; Comoletti et al., 2004). The neuroligin-3 R451C mutation is a gain of function mutation. Mice with this point mutation exhibited impaired social interactions and increased inhibitory synaptic transmission (Tabuchi et al., 2007). Mice lacking neuroligin-4 correspond to loss-of-function mutations in human neuroligin-4 and show deficits in reciprocal social interactions and ultrasonic communication (Jamain et al., 2008). Neuroligin 1/2/3α triple knock-out animals die at birth, but similar to their α-neurexin-deficient

counterparts, do not show dramatic reductions in synapse numbers or brain architecture, but do have severely impaired synaptic transmission (Varoqueaux et al., 2006).
The studies of the neurexin and neuroligin functions indicate a role for them in proper synaptic function but not synapse formation. Although it is clear that the deficits of neurexins and neuroligins play a role in ASD, understanding their interactions with receptors will provide additional insight into their functions.

6. Neurexins associate with multiple receptors, including nAChRs

Accumulating evidence indicates that neurexins interact directly with more than the neuroligins. Our laboratory was the first to provide experimental evidence for direct interactions between neurexins and receptors by showing that neurexin-1β coimmunoprecipitates with recombinant α4β2 nAChRs when expressed in heterologous cells (Cheng et al., 2009). Functionally, the neurexin-1β regulates targeting of α4β2 nAChRs to pre-synaptic terminals in neurons (Cheng et al., 2009). Complementary studies report a role for neurexin-1 and neuroligin-1 in recruitment of α3-containing nAChRs to the post-synaptic density (Conroy et al., 2007; Ross & Conroy, 2008). In addition, recent studies show that neurexins interact with multiple receptors. First, neurexin-1β interacts with $GABA_A$ receptors; this interaction modulates the cell surface expression levels of the $GABA_A$ receptors but not its functions *per se* (Zhang et al., 2010). Second, leucine-rich repeat transmembrane protein (LRRTM2) binds trans-synaptically to both neurexin-1α and-1β and induces presynaptic differentiation at excitatory synapses (Ko et al., 2009; de Wit et al., 2009; Siddiqui et al., 2010). Knock-down of LRRTM2 in the rat dentate gyrus shows a large reduction in AMPAR-mediated EPSCs in *in vivo* recordings from granule cells in hippocampal slices. Furthermore, the association between neurexin-1 and LRRTM2 is a functional interaction. When neurexin-1 is knocked-down in hippocampal neurons, LRRTM2 is unable to induce presynaptic differentiation (de Wit et al., 2009). Finally, neurexins associate with GluRδ2 receptors via a soluble protein called cerebellin -1 precursor protein (Cbln1) (Uemura et al., 2010). In the Cbln1 knockout mice, the synaptogenic activity of GluRδ2 receptor is lost. Thus, GluRδ2 mediates cerebellar synapse formation by interacting with presynaptic neurexins via Cbln1.

7. Genetic variants of neurexin-1 are linked to nicotine dependence

A recent high-density genome-wide association study for nicotine dependence linked single nucleotide polymorphisms (SNP) in the neurexin-1 gene to the development of nicotine dependence and thus smoking behavior (Bierut et al., 2007). A second independent study also showed linkage between a variant of the neurexin-1 gene and nicotine dependence in smokers of European and African-American ancestry (Nussbaum et al., 2008). These results, along with the fact that neurexins functionally target α4β2 nAChRs to synapses, implicate neurexins in the etiology of other neurological diseases typically associated with pathophysiological functions of nAChRs. α4β2 nAChRs mediate essential features of nicotine addiction including reward, tolerance, and sensitization (Tapper et al., 2004). Thus, functions are likely to be affected by changes in the expression levels of neurexin-1. The exact mechanism by which neurexin-1α and -1β splicing is regulated to generate the predicted hundreds of neurexin-1 isoforms remains to be elucidated. It is possible that a regulatory SNP in the intron of the neurexin-1 gene could modulate neurexin-1 expression

or splicing efficiency and thus influence nAChR functions by regulating their synaptic targeting efficiency. Because there are hundreds of neurexin-1α isoforms, the linkage between neurexin-1 gene variants, α4β2 nAChR synaptic targeting, and nicotine dependence requires additional studies. Nevertheless, the functional linkage between neurexin-1 and α4β2 nAChR and their converging roles in nicotine dependence suggests that α4β2 nAChR activity may regulate neurexin-1 gene expression.

8. nAChR modulate excitation-inhibition balance

There is strong evidence that some forms of ASD are caused by an imbalance of excitatory and inhibitory synaptic transmission in neuronal circuits that are responsible for the establishment of language processing and social behavior during prenatal and postnatal brain development. Increased glutamatergic (excitatory) signaling or suppressed GABAergic (inhibitory) signaling is sufficient to disrupt the excitatory/inhibitory balance in local circuit-plasticity (Rubenstein & Merzenich, 2003). A hyperexcitable cortex is poorly differentiated functionally and therefore inherently unstable and susceptible to epilepsy. This might explain why, in addition to the autistic core symptoms, an average of ~30% of individuals with ASD develop clinically apparent seizures (Gillberg & Billstedt, 2000). In several mouse models of autism this lack of homeostasis of excitatory and inhibitory signaling was observed (Tabuchi et al., 2007; Gogolla et al., 2009). In the frontal cortex, cholinergic transmission can modulate cortical tone establishing a homeostasis of excitatory and inhibitory signals (Aracri et al., 2010). In layer V of the prefrontal cortex, nAChR activation increases the threshold for activating glutamatergic synapses (Couey et al., 2007), whereas GABA release is stimulated in several cortical layers by nAChR activation (Alkondon et al., 2000).

We posit that some of the regulatory effects of balancing inhibitory and excitatory synaptic transmission are mediated by synaptic targeting of nAChRs by neurexins. This results in the change of expression levels of nAChRs in various brain regions of autistic individuals. Therefore allosteric modulators or direct agonists targeting nAChRs by might be useful to restore the imbalance of excitatory and inhibitory synaptic transmission caused by deregulated expression of neurexin-1.

9. Nicotinic receptors as biomarkers for ASD

9.1 Positron Emission Tomography ligands for α4β2 nAChRs

The alterations in nAChRs in ASD may also serve as an early molecular biomarker, detectable by imaging tools such as positron emission tomography (PET), the most advanced modality for non-invasive study of receptors. Monitoring the reversal of the loss of α4β2 nAChR in the frontal, parietal, and cerebellar cortex and the upregulation of α7 nAChR in the cerebellar cortex by PET imaging in the brains of individuals with ASD might provide a clinical tool to complement behavioral tests needed to assess the effectiveness of novel pharmacotherapies for autism.

Three radiotracers, [^{11}C]nicotine, (S)-3- (azetidin-2-ylmethoxy)-2-[^{18}F]fluoropyridine (2-[^{18}F]FA) and (S)-5- (azetidin-2-ylmethoxy)-2-[^{18}F]fluoropyridine (6-[^{18}F]FA), have been used for studying α4β2 nAChRs in the human brain using PET. The PET imaging properties of these radioligands are not perfect however. Poor signal-to-noise ratios and other drawbacks of [^{11}C]nicotine suggest that this radiotracer is not well suited for quantitative imaging in

animals and humans. 2-[^{18}F]FA is the only currently available radioligand for quantitative imaging nAChR in humans. The "slow" brain kinetics of 2-[^{18}F]FA and 6-[^{18}F]FA hamper mathematical modeling and reliable kinetic parameter estimation since it takes many hours of PET scanning (5–7 h) for the tracer radioactivity to reach a spatial-temporal steady state (Horti et al., 2010). Another crucial problem with 2-[^{18}F]FA and 6-[^{18}F]FA is relatively low binding potential (BP) in extrathalamic regions (BP ≤ 0.6–0.8), including the cortex, which has a lower nAChR density. Altered densities of cortical and striatal nAChRs in neurodegenerative diseases (Pimlott et al., 2004) and schizophrenia (Ochoa & Lasalde-Dominicci, 2007) illustrates the importance of imaging extrathalamic nAChRs.

A variety of radioligands with fast regional brain kinetics have been presented in non-human primates and pigs. Analogs of epibatidine showed "rapid" brain kinetics and improved BP (Gao et al., 2007, 2008). One compound of the series, (-)-2-(6-[^{18}F]fluoro-2,3'-bipyridin-5'-yl)-7-methyl-7-aza-bicyclo[2.2.1]heptane ([^{18}F]JHU87522 or [^{18}F]AZAN) exhibited better imaging properties in animal studies than those of 2[^{18}F]FA and 6-[^{18}F]FA including a greater BP value and faster brain kinetics. In addition, the brain uptake of [^{18}F]AZAN is greater and its acute toxicity is lower. Most available PET and single photon emission computed tomography (SPECT) imaging agents for nAChR are agonists and these nAChR-agonists are toxic when injected at high doses. Unlike 2-FA that is nAChR agonist, AZAN displays properties of functional antagonist of α4β2 nAChR. Currently, AZAN is undergoing toxicological studies that will determine if this radioligand is sufficiently safe for clinical application as a PET radiotracer. If [^{18}F]AZAN is safe for human PET studies, there are strong indications that it could become the radiotracer of choice for PET imaging of nAChR in human brain (Horti et al., 2010).

9.2 Positron Emission Tomography ligands for α7 nAChRs

Several radiotracers were developed for selective imaging of the α7 nAChRs in the human brain for PET and SPECT (Dolle et al., 2001; Pomper et al., 2005; Ogawa et al., 2006). Despite these efforts, there have been no clinical studies using these radioligands for α7 nAChRs in the human brain.

Very recently, 4-[^{11}C]methylphenyl 2,5-diazabicy- clo[3.2.2]nonane-2-carboxylate ([^{11}C]CHIBA-1001) was developed as a novel PET ligand for α7 nAChRs in the conscious monkey brain. An *in vitro* binding study showed that the IC_{50} value of CHIBA-1001 for [^{125}I]α-bungarotoxin binding to the rat brain homogenates was 45.8 nM. [^{11}C]CHIBA-1001 distribution in the monkey brain measured by PET was consistent with the regional distribution of α7 nAChRs. Moreover, brain uptake of [^{11}C]CHIBA-1001 was dose-dependently blocked by pretreatment with the selective α7 nAChR agonist SSR180711, but was not altered by the selective α4β2 nAChR agonist A-85380 (Hashimoto et al., 2008).

In the human brain, [^{11}C]CHIBA-1001 was found widely distributed in all brain regions. The regional distribution pattern of [^{11}C]CHIBA- 1001 is consistent with what is expected *in vitro* (Falk et al., 2003; Court et al., 1999; 2001; Marutle et al., 2001), but different from that of α4β2 nAChRs (Clementi, 2004). However, it is slightly different from the regional distribution in the monkey brain (Hashimoto et al., 2008). In the human brain, remarkable radioactivity accumulation was observed in the cerebellum. These findings suggest that [^{11}C]CHIBA-1001 is a suitable radioligand for imaging α7 nAChRs in the human brain, as it offers acceptable dosimetry and pharmacological safety at the dose required for adequate PET imaging (Toyohara et al., 2009).

These recent advances in the development of new nAChR PET radioligands, like [^{18}F]AZAN for α4β2 nAChRs and [^{11}C]CHIBA-1001 for α7 nAChRs with fast kinetics and low toxicity will provide promising tools for monitoring alterations of brain nAChR especially in young patients with ASD. The principal downside to the use of PET is the unknown risk of using radioactive ligands and sedatives, especially in younger individuals, to perform PET scans.

10. Nicotinic drugs as therapeutic agents for ASD

10.1 Agonists

10.1.1 α4β2 nAChRs

The extensive loss of α4β2 nAChRs in some individuals with ASD provide a rationale for exploratory trials of drugs that can upregulate and activate α4β2 nAChRs and thus compensate for their loss both physically and functionally. The panoply of drugs developed over the last few decades for smoking cessation therapy as well as other disorders with pathophysiological roles for nAChRs (Taly et al., 2009), offers a large selection of drugs that are likely to be specific for α4β2 nAChRs and capable of upregulating them. Varenicline (Chantix), one such drug that has FDA approval for use in smoking cessation therapy is a partial agonist of the α4β2 nAChRs (Coe et al; 2005) and of interest for treatment of ASD. Although varenicline is also a full agonist of the α7 AChR (Mihalak et al., 2006), its relative specificity for α4β2 nAChRs is thought to be due to differences in its EC_{50} for activation of α4β2 nAChRs versus α7 nAChRs, as well as a function of the low concentrations at which it is used clinically for anti-smoking therapy (Niaura et al., 2006). Thus it has become one of the most widely used smoking cessation drugs with millions of users worldwide and shows little sympathetic and parasympathetic complications from cross activation of ganglionic nAChRs (α3β4 nAChRs). Interestingly, much like nicotine, varenicline can upregulate α4β2 nAChRs *in vitro*. Finally, as a partial agonist, it has the additional benefit of providing chronic low-level activation of α4β2 nAChRs (Papke et al., 2011) and possibly associated downstream intracellular signaling pathways. Varenicline has been shown to change behaviors in some smokers, and a public health advisory from the FDA includes warnings of increased suicidal thoughts and actions. It is important to note, however, that the increase in suicidal thoughts and actions may occur in only a subpopulation of individuals taking varenicline as there is ample evidence that smoking may be more prevalent in those individuals with comorbid neuropsychiatric conditions, including schizophrenia (Adler et al., 1993; Dalack et al., 1999). This may explain behavioral changes reported among smokers using varenicline if individuals have subclinical neuropsychiatric conditions. This idea has been supported by a recent study reporting that there was no clear evidence that varenicline use in itself was associated with an increased risk for depression or suicidal thoughts (Gunnell et al., 2010). Also, unlike in schizophrenia, the prevalence of smoking in individuals with ASD is low (Bejerot & Nylander, 2003), possibly because the loss of α4β2 nAChRs occurs early in development – a clinical feature further strengthening the utility of using α4β2 nAChRs loss as a biomarker for ASD. Nevertheless, any clinical trial of varenicline for individuals with ASD should require close monitoring of possible suicidal ideation given the heterogeneity of causes expected for ASD, some of which may overlap with schizophrenia (Kirov et al., 2009).

10.1.2 α7 nAChRs

It is possible to use α7 nAChR agonists to treat neuroinflammation in ASD. There is strong evidence that activation of the α7 nAChR expressed on monocytes and macrophage, by inhibiting NF-kappaB nuclear translocation, suppresses cytokine release by them (Wang et al., 2003), and that this cholinergic anti-inflammatory pathway that provides a bidirectional link between the nervous and immune system, inhibits the innate immune response (Rosas-Ballina & Tracey, 2009). Hence, a reasonable case can be made for the use of α7 nAChR agonists to treat neuroinflammation in ASD. Individuals could be stratified by monitoring brain inflammation by the uptake of the microglial marker, [^{11}C]PK11195, a PET ligand useful for detecting peripheral benzodiazepine receptors expressed in high amounts in activated microglia (Rojas et al., 2007). However, given that α7 AChR appears to be pathologically upregulated in cerebellum of some individuals with ASD, caution is advocated in the use of α7 AChR agonists to treat ASD. The primary challenge is that the net behavioral benefit from suppressing neuroinflammation mediated by microglia versus over stimulating upregulated α7 AChRs in the granule cell layer, cannot be predicted *a priori*. Two different α7 nAChR agonists have been used to treat schizophrenia; drugs that might be repurposed for use in individuals with ASD and detectable neuroinflammation.

One of these drugs, GTS-21, or 3-(2,4-dimethoxybenzylidene)-anabaseine (DMXB-A) is a partial agonist of α7 nAChRs may have beneficial effects in ASD patients. In healthy control subjects, DMXB-A improves attention, working memory, and episodic memory (Kitagawa et al., 2003). The default network, which has been widely reported to be abnormal in schizophrenia (Garrity et al., 2007), is a functionally connected network of brain regions that includes the posterior cingulate cortex, cuneus/precuneus, medial prefrontal cortex, medial temporal lobe, and inferior parietal cortices (Buckner et al., 2008; Tregellas et al, 2011). Altered default network activity has been shown to be a result of DMXB-A administration to patients with schizophrenia (Tregellas et al., 2011), with decreased expression of α7 nAChRs (Freedman et al., 1995).

A second candidate drug, Tropisetron is a partial agonist of the α7 nAChR. Auditory sensory gating P50 deficits are correlated with neuropsychological deficits in attention, one of the principal cognitive disturbances in schizophrenia. In a clinical trial with 33 schizophrenic patients administration of tropisetron, without placebo, significantly improved auditory sensory gating P50 deficits in non-smoking patients with schizophrenia (Shiina et al., 2010). In mice, the early postnatal period represents a critical time window essential for brain development. The administration of tropisetron from postnatal days 2-12 (P2-P12) in mice did not induce significant cognitive, schizophrenia-like or emotional alterations in tropisetron-treated animals as compared to controls, when tested in multiple behavioral assays (Inta et al., 2011).

10.2 Positive allosteric modulators

Galantamine is an acetylcholinesterase inhibitor that also acts as a positive allosteric modulator at the α4β2 and α7 nAChRs (Dajas-Bailador et al., 2003; Samochocki et al., 2003; Schilström et al., 2007). In two studies with small numbers of subjects it has been reported that galantamine showed potential benefits for attention, memory, and psychomotor speed in schizophrenia (Schubert et al., 2006; Lee et al., 2007). An unpublished study from Johnson and Johnson failed to find an advantage for galantamine on a measure of global cognition

(clinicaltrials.gov, trial number: NCT 00077727). In a 12-week open-label trial of galantamine, thirteen children with autism, previously unmedicated, (mean age, 8.8 +/- 3.5 years) showed a significant reduction in parent-rated irritability and social withdrawal on the Aberrant Behavior Checklist (ABC), as well as significant improvements in emotional lability and inattention on the Conners' Parent Rating Scale—Revised (Nicolson et al., 2006). Similarly, clinical ratings showed reductions in the anger subscale of the Children's Psychiatric Rating Scale. Eight of 13 participants were rated as responders on the basis of their improvement scores on the Clinical Global Impressions scale. The allosteric properties of galantamine could directly lead to increased release of acetylcholine and activation of postsynaptic nAChRs (Samochocki et al., 2003) or act indirectly through its effects on the release of other neurotransmitters, especially glutamate and dopamine (Schilström et al., 2007; Wang et al., 2007).

It has been demonstrated that amyloid-β precursor protein (APP) is upregulated in a mouse model for Fragile X mental retardation (FXS) (Westmark et al., 2008) and two clinical studies have reported higher levels of APP in children with autism. In the first study, affected children expressed sAPP at 2 or more times the levels of children without autism and up to 4 times more than children with mild autism (Sokol et al., 2006). In the second study, elevated plasma sAPPα was found in 60% of known autistic children (n = 25) compared to healthy age-matched controls (Bailey et al., 2008). Recent studies showed that galantamine allosterically modulates microglial nAChRs and increases microglial beta-amyloid (Aβ) phagocytosis (Wang et al., 2007; Takata et al., 2010).

Collectively, these studies suggest that positive allosteric modulators of α4β2 nAChRs, when used by themselves or in conjunction with agonists, may be beneficial in correcting deficits in the functions of α4β2 nAChRs and thereby core deficits of ASD.

11. Conclusions

This review presents a reasonable rationale based on synthesis of the literature that nAChRs are suitable biomarkers as well as therapeutic targets for addressing core deficits in ASD. Multiple lines of evidence show that nAChRs can modulate many of the functions deficient in individuals with ASD. Furthermore, neuropathological findings, albeit small in numbers, show significant alterations in both α4β2 nAChRs and α7 nAChRs. In the cerebellum, an anatomical area contributing significantly to the etiology of ASD, α4β2 nAChRs are deficient, and α7 nAChRs are upregulated. These findings suggest that well developed PET ligands for both these nAChR subtypes can be used to monitor changes in their expression in response to treatment, behavioral or pharmacological. A novel functional linkage between neurexin-1 and α4β2 nAChR and their converging roles in nicotine dependence suggests that α4β2 nAChR activity may regulate neurexin-1 gene expression. Additionally, agonists and positive allosteric modulators of the α4β2 AChRs are likely to be therapeutic agents that can help restore α4β2 nAChRs expression levels in the brains of individuals with ASD, based on known effects of these agents. A case can be made for the use of α7 nAChRs to reduce neuroinflammation in the brain in those ASD individuals with such clinical pathology. The ultimate hope is that these agents, when administered early in development, by their presumed ability to modulate a number of different neurotransmitter systems and associated signaling pathways, could help correct core deficits associated with ASD.

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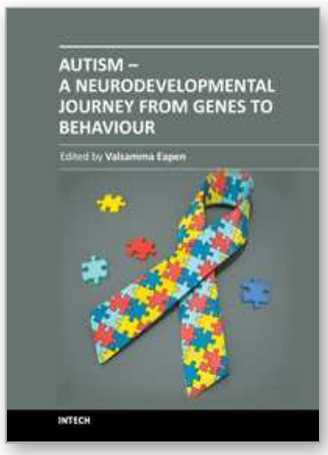

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The book covers some of the key research developments in autism and brings together the current state of evidence on the neurobiologic understanding of this intriguing disorder. The pathogenetic mechanisms are explored by contributors from diverse perspectives including genetics, neuroimaging, neuroanatomy, neurophysiology, neurochemistry, neuroimmunology, neuroendocrinology, functional organization of the brain and clinical applications from the role of diet to vaccines. It is hoped that understanding these interconnected neurobiological systems, the programming of which is genetically modulated during neurodevelopment and mediated through a range of neuropeptides and interacting neurotransmitter systems, would no doubt assist in developing interventions that accommodate the way the brains of individuals with autism function. In keeping with the multimodal and diverse origins of the disorder, a wide range of topics is covered and these include genetic underpinnings and environmental modulation leading to epigenetic changes in the aetiology; neural substrates, potential biomarkers and endophenotypes that underlie clinical characteristics; as well as neurochemical pathways and pathophysiological mechanisms that pave the way for therapeutic interventions.

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