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The role of beta-adrenergic receptor blockers in autism

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Abstract: β-adrenergic receptor blockade has been demonstrated to benefit individuals with autism. Genetic studies have identified numerous factors linking β-adrenergic receptor blockade to autism spectrum disorder (ASD), including β-adrenergic receptor variants, human leukocyte antigen genes, apoptotics factor caspase-3, glycogen synthetase kinase-3β, and the reduced form of nicotinamide adenine dinucleotide phosphate. β-adrenergic receptor blockade has also been implicated in ASD via its effects on myelin basic protein, prostaglandins, cyclooxygenase-2, and nitric oxide synthase. β-adrenergic receptor blockade may have a significant role in ASD.Therefore, the characterization of β-adrenergic receptor blockade in individuals with ASD is needed.

Keywords: B-Adrenergic Receptor Blocker, Autism, Autism Spectrum Disorder, B-Adrenergic Receptor Antagonism

1. Introduction

Autism spectrum disorder (ASD) is a childhood-onset neuro-developmental disorder characterized by disturbances in social interactions, imaginative activities, communication, and speech. A significant association between β-adrenergic receptors and autism has been demonstrated. In the brain, β-adrenergic receptors are widely distributed in different regions, including the frontal, parietal, piriform, and retrosplenial cortices; medial septal nuclei; olfactory tubercle; midbrain; striatum; hippocampus; and thalamic nuclei [1-2]. In behavioral tests, newborn rats that were given the β_2-adrenoceptor agonist terbutaline (10 mg/kg) daily on post-natal days 2 to 5 showed consistent patterns of hyper-reactivity to novel and aversive stimuli when assessed in a novel open field, as well as in the acoustic startle response test [3]. These findings indicate that β_2-adrenoceptor over-stimulation during an early critical period results in microglial activation associated with innate neuro-inflammatory pathways and behavioral abnormalities, similar to those described in autism. Term children exposed to tocolysis exhibited a higher rate of psychiatric disorders and poorer cognitive and motor performance than controls [4]. Plasma and urine norepinephrine (NE) levels were increased in ASD patients [5-6]. Individuals with ASD performed more poorly than non-ASD individuals on the working memory test. Importantly, the administration of propranolol attenuated this impairment, with the ASD group performing significantly better under the propranolol condition than the placebo condition [7]. These findings suggest that NE may play a role in cognitive impairment associated with ASD. Ratley et al. [8] began open trials of β-adrenergic receptor blockers, as adjunctive medication in eight consecutive autistic adults. The immediate result across all patients was a rapid diminution in aggressive behavior. As time on the drug increased, subtler changes in speech and socialization emerged. Narayanan et al. [9] demonstrated a potential imaging marker for the cognitive effects of propranolol in ASD. Propranolol significantly improved performance in word fluency, but not letter fluency among autism participants [10-11]. More difficult taskswere performed while on propranolol (40 mg) than on placebo; the benefit of β-adrenergic receptor blockade depends on the difficulty of the cognitive flexibility task and the individual's ability to solve these types of tasks under unstressed conditions [12]. These findings suggest that β-adrenergic receptor blockade may play a role in autism. In this paper, we discuss the potential role of β-adrenergic receptor blockers in autism.

2. The Genetic Role of β-adrenergic Receptor Blockers in Autism

2.1. β-Adrenergic Receptor Variants

Genetic studies provide an excellent opportunity to link molecular variations with epidemiological data. DNA sequence variations, such as polymorphisms, have modest and subtle biological effects. Receptors play a crucial role in the regulation of cellular function, and small changes in their structure can influence intracellular signal transduction pathways. The mechanism by which genetic susceptibility to over-stimulation of the β-adrenergic receptor is conferred may increase the risk for alterations, such as those that that lead to autism, in neuro-development. Connors et al. [13] found high frequencies of the *Gly16* and *Glu27* alleles in the *β-adrenergic receptor* polymorphisms in individuals with autism. In the Autism Genetic Resource Exchange (AGRE) population, the *Glu27* allele of the *β_2-adrenergic receptor* gene also conferred an increased risk of autism [14].

2.2. The Human Leukocyte Antigen (HLA)

Studies have suggested that HLA genes are located in the major histocompatibility complex (MHC) class II molecule region. HLA genes have been implicated in autism susceptibility. A number of cellular activation markers, including HLA-DR and CD26 on T cells, were significantly increased in an autism group compared with controls [15]. *HLA-DRB1* has been associated with autism in Caucasians and Han Chinese [16-20]. Higher frequencies of the *DR4* allele have been shown to exist in autistic Caucasians [21-22], but the frequencies were lower in autistic Han Chinese compared with controls [20]. The *HLA-DR4* gene may be expressed in the mothers of children with autism during pregnancy, contributing to autism in their offspring [21]. The *DR13* allele is also associated with autism in Caucasians [17] but not in Han Chinese [20]. Patients with autism and the *DR4*, *DR11*, or *DR14* alleles performed differently on intelligence and neuro-psychology tests compared with controls [20]. The haplotype *B44-SC30-DR4* was also associated with autism in Caucasians [22-23]. Moreover, a correlation between *HLA-DR* and *HLA-DQ* gene polymorphisms and the anti-β-receptor antibodies in familial cardiomyopathy has been suggested [24]. Cardiac β-adrenergic receptors and adenylatecyclase activity in dilated cardiomyopathy have been shown to be modulated by circulating autoantibodies against the cardiac β_1-adrenoceptor, the presence of which isregulated bythe HLA-DR gene [25]. Propranolol abrogated interferon-gamma (IFN-ɤ)-induced increases in HLA class II expression and interleukin-1beta (IL-1β) secretion [26]. HLA-DR expression was significantly reduced in the lymphocytes of carvedilol-treated congestive heart failure (CHF) patients [27]. These findings suggest that β-adrenergic receptor blockers may affect ASD via the suppression of MHC class II antigen expression.

2.3. Apoptotic Factor Caspases

Caspases are cysteinyl aspartate-specific proteases that play a critical role in the regulatory and execution phases of apoptosis [28]. Neonatal exposure to sevoflurane, an anesthetic, significantly increased the number of apoptotic cells and increased cleaved caspase-3 in the brain. Sevoflurane also induced abnormal social behaviors and deficits in mouse fear conditioning [29]. Caspase-3 increased in the cerebella of participants with autism [30]. The expression of caspases also increased in the peripheral blood mononuclear cells of patients with ASD [31]. Moreover, β_1-selective adrenoceptor antagonism effectively inhibited NE-induced apoptosis in adult rat ventricular myocytes [32]. D-propranolol suppressed caspase-3 activation by 63% and preserved cell survival to 88% of the control value in cases of lysosomal iron accumulation and oxidative injury in endothelial cells [33]. β-adrenoceptor blockers protect against staurosporine-induced apoptosis in SH-SY5Y neuroblastoma cells. Propranolol and ICI 118551, but not atenolol, demonstrated a concentration-dependent inhibition of caspase-3-like activity [34]. These findings suggest that β-adrenergic receptor antagonists may influence the onset of autism through the suppression of apoptotic factor caspase-3.

2.4. Glycogen Synthetase Kinase-3β (GSK3β)

GSK3β is a protein kinase that is involved in many physiological processes (e.g., metabolism, gene expression and apoptosis). GSK3β is pivotal in controlling neuronal polarity within primary embryonic hippocampal neurons [35]. Mice with a fragile X retardation 1 (*Fmr1*) gene deletion are used to model autistic behaviors. The inhibitory serine phosphorylation of GSK3β is lower in the brain regions of *Fmr1* knockout mice than in those of wild-type mice [36]. The impaired inhibition regulation of GSK3β in *Fmr1* knockout mice may contribute to some socialization deficits, and lithium treatment can ameliorate certain socialization impairments [36-38]. The expression of mutant *Tph2* in mice results in a marked reduction (~80%) in brain serotonin (5-HT) production and leads to behavior abnormalities in emotional states. GSK3β activation accompanies this reduction in brain 5-HT levels. The inactivation of GSK3β in *Tph2* knock-out mice, either using pharmacological or genetic approaches, alleviates the aberrant behaviors produced by a 5-HT deficiency [39]. Furthermore, the Wnt/β-catenin pathway plays a critical role in the proliferation, differentiation, apoptosis, and cell outgrowth processes of the CNS during embryonic development [40]. The dysregulation of the Wnt pathway may contribute to the pathogenesis of neurodevelopmental disorders such as autism. Sundilac, an inhibitor of the Wnt/β-catenin pathway, decreased activated GSK3β levels and ameliorated repetitive/stereotypic activity, as well as the learning, memory, and behavioral abnormalities found in rat autism models [41]. Moreover, constitutive GSK3β activity protects against chronic β-adrenergic remodeling of

the heart [42]. Propranolol restores cognitive deficits and improves amyloid and Tau pathologies in a senescence-accelerated mouse model, which was associated with an increase in GSK3β phosphorylation [43-44]. Taken together, these findings suggest that β-adrenergic receptor blockers may play a role in autism by modulating GSK3β activity.

2.5. The Reduced Form of the Nicotinamide Adenine Dinucleotide Phosphate (NADPH) Oxidase (NOX) Enzyme Complex

NOX mediates critical physiological and pathological processes including cell signaling, inflammation and mitogenesis, by generating reactive oxygen species (ROS) from molecular oxygen. Mitochondrial dysfunction and altered energy metabolism may influence the social and cognitive deficits present in patients with autism. The NOX activity in the lymphocytic mitochondria of children with autism was significantly lower than that in controls [45]. Levels of plasma ATP and red blood cell NADH were reported to be lower in children with autism than in controls. Vitamin and mineral supplements were associated with a greater significant improvement in ATP and NADH levels, as well as hyperactivity, tantrum, and receptive language subscores, in the autism group compared with the placebo group [46-47]. In addition, gene variants of the NADH-ubiquinone oxido-reductase 1αsubcomplex 5 (NDUFA5), an enzyme complex in the mitochondrial electron transport chain, are associated with autism [48]. Moreover, nebivolol, a third-generation selective β_1-adrenoceptor, improved left ventricle dysfunction and survival immediately after myocardial ischemia and inhibited cardiac NOX activation [49]. Nebivolol treatment has been associated with improvements in insulin resistance, reduced proteinuria and NOX activity, and the production of reactive oxygen speciesin the kidneys and skeletal muscle tissue of transgenic TG (mRen2)27 rats (Ren2) [50-51]. Nebivolol also improved diastolic relaxation, fibrosis,and remodeling in obese Zucker rats, and reduced NOX-dependent superoxide production [52]. Carvedilol attenuated the increased expression of NOX subunits in the hearts and kidneys of rats after daunorubicin-induced cardiotoxicity and nephrotoxicity [53]. NOX activity in whole blood and isolated neutrophils was dose-dependently inhibited by nebivolol, whereas atenolol, metoprolol, and carvedilol were markedly less effective in Watanabe heritable hyperlipidemic rabbits [54]. Celiprolol, a specific β_1-receptor antagonist with weak β_2-receptor agonistic activity, suppressed NOX $p22^{phox}$, $p47^{phox}$, gp91phox, and Nox1 expression in the left ventricle of deoxycorticosterone acetate (DOCA)-salt hypertensive rats [55].Taken together, these findings suggest that β-adrenergic receptor antagonists play a role in autism through the suppression of NADPH expression.

3. The Non-genomic Role of β-adrenergic Receptor Blockers in Autism

3.1. Myelin Basic Protein (MBP)

Immune comorbidities often are reported in subsets of patients with neuro-developmental disorders, including ASD and attention-deficit hyperactivity disorder. A common immunopathology is an increase in serum autoantibodies against neuron-axon filament protein (anti-NAFP), glial fibrillary acidic protein (anti-GFAP) and MBP relative to control patients. Increases in autoantibodies suggest possible deficits in self-tolerance that may contribute to the formation of brain-specific autoantibodies and subsequent effects on the central nervous system (CNS) [56-57]. In midline structures including the region of the absent corpus callosum of BTBR mouse model of autistic-like behavior revealed selective changes in neurodevelopmental proteins and adult hippocampal neurogenesis; the myelin markers 2', 3'-cyclic nucleotide 3'-phosphodiesterase (CNPase) and MBP were reduced [58]. A magnetization transfer imaging study of corpus callosum myelination was significantly higher in children with autism than in typically developing children, suggesting abnormal myelination of the corpus callosum in autism [59]. Autistic children had significantly higher serum levels of serotonin and anti-MBP auto-antibodies than healthy children. However, serum serotonin levels had no significant correlations with serum levels of anti-MBP auto-antibodies in autistic patients [60]. Markham et al. [61] demonstrated that the sensitivity of myelination to experience is reduced in adulthood relative to development in both sexes. High serum anti-NBP antibodies were reported in Egyptian autistic children [62]. Antibodies MBP against fetal brain were revealed in sera of mothers with autistic children [63]. Transmission disequilibrium study suggested that an oligodendrocyte and myelin glycoprotein gene allele was associated with families with an autistic proband [64]. However, high-affinity muscarinic cholinergic receptors were detected in myelin purified from rat brain stem with use of the radioligands 3H-N-methylscopolamine (3H-NMS), 3H-quinuclidinyl benzilate (3H-QNB), and 3H-pirenzepine. 3H-NMS binding was also present in myelin isolated from corpus callosum [65]. The possibility that some of these muscarinic receptors may be involved in regulation of phosphinositide metabolism and the protein kinase activities of myelin is considered. A novel clonal cell line derived from a human glioma (HOG) was found to express some oligodendrocyte-specific proteins including a 15-kDa form of myelin basic protein (MBP) and high 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase) activity. Receptor types expressed by HOG cells included A_2-adenosine, prostaglandin E1, and β_2-adrenergic receptors linked to stimulation of adenylatecyclase [66]. Vroon et al. [67] demonstrated that induction of experimental autoimmune

encephalomyelitis (EAE) by myelin oligodendrocyte glycoprotein (MOG) resulted in a profound decrease in G-protein-coupled receptor kinases (GRK), including GRK2 and GRK6 protein, in splenocytes during all phases of disease. *GRK2* mRNA was also lower during EAE. Canine distemper (CD) virus primarily infects astrocytes and causes a demyelinating disease in dogs that closely resembles multiple sclerosis (MS). In control dogs, including three dogs with another inflammatory disease, β_2-adrenergic receptor immuno-reactivity was observed on both neurons and astrocytes. In dogs with CD encephalitis, β_2-adrenergic receptors were present on neurons, but were absent on astrocytes in acute lesions, demyelinated lesions, and normal-appearing white matter [68]. In MS, De Keyser et al. [69] found that astrocytes, not only in plaques but also in normal-appearing white matter, lack β_2-adrenergic receptors. This abnormality might play a crucial role in the pathophysiology of MS. Taken together, β_2-adrenergic receptor blockers may have a role in autism by modulating myelin formation.

3.2. Prostaglandins (PGs) and Cyclooxygenase (COX)

PGs play a role in inflammatory processes. COX participates in the conversion of arachidonic acid into PGs. These released prostanoids play an important role in normal neural function, including spatial learning, synaptic plasticity and long-term potentiation [70]. The PGE_2 signaling pathway may have an important role in early development; the expression of four EP (E-prostanoid) receptor' transcripts (EP_1, EP_2, $EP_3\beta$, and EP_4) significantly increases in mouse embryos from Days 11-15 [71]. The normal laminar pattern of COX-2 expression- in the human cortex is altered in patients with Rett syndrome, a type of ASD [72]. There is an association between the *PTGS2* polymorphism (the gene that encodes the COX-2 enzyme) and Korean trios with ASD [73]. Moreover, epinephrine increases the release of PGE_2 in human colon adenocarcinoma HT-29 cells, which can be blocked by COX-2 inhibitors or atenolol and ICI 118,551 (β_1- and β_2-selective receptor adrenergic antagonists, respectively) [74]. β_2-adrenergic receptor antagonists suppress COX-2 expression in pancreatic cancer cells [75]. Propranolol inhibited cell proliferation and repressedgastric cancer cell growth through the downstream COX-2 pathway [76-77]. In addition, the administration of propranolol and a COX-2 inhibitor, which can be applied peri-operatively in most cancer patients with minimal risk and low cost, counteracted several immunological and endocrinological perturbations and improved recurrence-free survival rates in mice undergoing primary tumor excision [78-79].These findings suggest that β-adrenergic receptor antagonists may play a role in modulating the inflammatory process in ASD.

3.3. Reactive Oxygen Species (ROS)

ROS play a major role in various cell-signaling pathways. ROS activate various transcription factors and increase the expression of proteins that control cellular transformation, tumor cell survival, tumor cell proliferation and invasion, angiogenesis, and metastasis. Lipid peroxidation is a chain reaction between polyunsaturated fatty acids and ROS, and it produces both lipid peroxides and hydrocarbon polymers, which are highly toxic to the cell. Malonyldialdehyde (MDA) is an end product of the peroxidation of polyunsaturated fatty acids. Lipid peroxidation is elevated in individuals with autism. The plasma MDA level is significantly higher in individuals with autism than in their siblings without autism [80]. Higher serum MDA and 8-hydroxy-2-deoxyguanosine (8OHdG) levels were found in children with autism compared with controls [81]. 8OHdD levels were also increased in the cerebellum of patients with autism [82-83]. The F_2-isoprostane 8-iso-prostaglandin $F_2\alpha$ is enhanced in children with autism [84].This isoprostane is a product of nonenzymatic oxidation of arachidonic acid and suggested as a marker of lipid peroxidation. Compared with controls, children with autism had significantly higher urinary levels of isoprostane $F_2\alpha$-VI (2,3-dinor-thromboxane B_2, a marker of lipid peroxidation) and 6-keto-prostaglandin $F_1\alpha$ [85]. The erythrocyte superoxide dismutase (SOD) activity in children with autism was significantly lower than that in normal controls [86]. The glutathione (GSH) plays an important role in a several cellular process including cell differentiation, proliferation, and apoptosis. GSH content was significantly lower in patients with autism compared with the control group [82, 87]. Moreover, myocardial tissue sections display increased ROSlevels after traumatic brain injuries. Treatment with propranolol reduced cardiac ROS levels [88]. D-propranolol attenuated lysosomal iron accumulation and oxidative injury in endothelial cells [33]. Carvedilol modulated ROS-induced signaling, and it significantly reduced ischemia-reperfusion-induced free radical production and NAD^+ catabolism, lipid peroxidation and red blood cell membrane damage, as determined by the assessment of free MDA production in heart perfusion and rheological models [89]. Carvedilol also protected against colcichine- and aluminum-induced neuro-toxicity in rats by attenuating oxidative stress, including lipid peroxidation, and nitrite concentration; restoring reduced GSH, SOD, catalase, and GSH S-transferase activity; and improving the memory performance of rats in the Morris water maze test [90-91]. Nebivolol improved diastolic dysfunction and myocardial remodeling by reducing oxidative stress in the transgenic (mRen2) rat [92]. These findings suggest that β-adrenergic receptor antagonists modulate oxidative stress in autism.

3.4. Nitric Oxide Synthase (NOS)

NOS is an enzyme involved in the synthesis of nitric oxide (NO), which regulates a variety of important physiological responses including cell migration, immune responses, and apoptosis. NO affects the development and function of the CNS. Specifically, NO enhances the release of dopamine in the striatum in animal models [93].

Extracellular dopamine increased following the intrastriatal infusion of NOS substrate [94]. Increased RBC NO levels and plasma GSH peroxidase (GSH-Px) were detected in patients with autism [95]. In addition, GSH plasma levels were decreased in children with autism compared with age-matched controls [96-97]. GSH pathway gene variations are associated with ASD [98-100]. Moreover, metipranolol suppressed NO-induced lipid peroxidation in the eyes and retinas of rats [101]. Nebivolol prevented vascular NOS III uncoupling in experimental hyperlipidemia [54]. Propranolol suppressed hemangioma growth through the inhibition of eNOS protein expression and the subsequent production of nitric oxide [102]. Celiprolol activated eNOS through the PI3K-Akt pathway via oxidative stress-induced NF-κBactivity [55]. These findings suggest that β-adrenergic receptor antagonists may play a role in ASDvia the inhibition of NOS expression.

4. Conclusion

β-adrenergic receptor blockade may play a role in ASD. Genetic studies have aided the identification of proteins that link β-adrenergic receptor antagonism to the pathology ofASD, including β-adrenergic receptor variants, human leukocyte antigen genes, apoptotics factor caspase-3, glycogen synthetase kinase-3β, and the reduced form of nicotinamide adenine dinucleotide phosphate. β-adrenergic receptor inhibition also affects ASD via non-genomic mechanisms, including myelin basic protein, prostaglandins, cyclooxygenase-2, and nitric oxide synthase. Thus, further examination of the relationship between β-adrenergic receptor antagonistsandASD is required.

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