

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



L1-79 and the Role of Catecholamines in Autism

John Rothman

Abstract

A growing body of evidence supports a role for catecholaminergic dysfunction in the core symptoms of autism spectrum disorder (ASD). This paper reviews the direct and indirect role of catecholamines on the central and peripheral nervous systems in ASD. Catecholamines innervate every tissue in the body and almost all tracts of the brain, providing a common neurologic regulatory mechanism for all ASD symptoms. Because the morphology of the catecholaminergic synapse is regulated by growth factors that are released contemporaneously with neurotransmitters, an event that results in abnormally large catecholamine release, will also release high levels of growth factors, which can result in the budding and arborization of nerve terminals. Here, we hypothesize that a hypertrophic synaptic morphology can occur in catecholaminergic systems and increase catecholaminergic tone throughout the body, resulting in an imbalance between catecholaminergic neurologic mechanisms and those that oppose them, and consequently pathology. By exerting a presynaptic effect to inhibit tyrosine hydroxylase and thus the synthesis, storage and release of all catecholamines, L1-79 (a tyrosine hydroxylase inhibitor) may diminish neurotransmitter release and its associated growth factors exerting a therapeutic effect on ASD by reducing the hypertrophic morphology of the synapse and bringing catecholamines back into a homeostatic balance with oppositional neurologic and metabolic influences.

Keywords: autism, autism spectrum disorder, catecholamines, D, L- α -methyl-para-tyrosine, L1-79

1. Introduction

Childhood autism is more prevalent than childhood cancer, juvenile diabetes and pediatric AIDS combined, with an estimated prevalence of 3 M children in Europe, 1.5 M in the US, and tens of millions throughout the rest of the world. More disturbing is that for no explicable reason childhood autism appears to be increasing at a rate of 10–17% per year [1]. Typically displayed in early childhood, autism may be associated with many co-morbidities that include epilepsy, attention deficit/hyperactivity disorder (ADHD), abnormal sensory or motor responses, disturbed sleep, reduced cognitive functionality, anxiety and aggression [2–4], or none at all.

In 2019 the CDC reported the rate of autism in the US to be 1 in 59 children, with boys being 4 times more susceptible than girls [5]. This means that 1 in 42 boys are diagnosed with autism. There was an increase of about 30% since the assessment of autism prevalence conducted previously (**Table 1**), and more almost 3x the rate that was reported only 20 years ago. In New Jersey the observed rate of autism was

Identified Prevalence of Autism Spectrum Disorder				
ADDM Network 2000-2010				
Combining Data from All Sites				
Surveillance Year	Birth Year	Number of ADDM Sites Reporting	Prevalence per 1,000 Children (Range)	This is about 1 in X children...
2000	1992	6	6.7 (4.5–9.9)	1 in 150
2002	1994	14	6.6 (3.3–10.6)	1 in 150
2004	1996	8	8.0 (4.6–9.8)	1 in 125
2006	1998	11	9.0 (4.2–12.1)	1 in 110
2008	2000	14	11.3 (4.8–21.2)	1 in 88
2010	2002	11	14.7 (5.7–21.9)	1 in 68

Table 1.
CDC: Prevalence of autism in the US [5].

1 in 46 children, which means that 1 in 29 boys born in New Jersey are likely to be autistic [6, 7].

The lifetime cost of raising an autistic child was estimated in 2014 to be \$3.2 M more than the cost of raising a non-autistic child [8], and this does not take into account the societal costs of maintaining these this population as adults once their families are no longer able to do so. The societal costs of autism are broad and deep, and many have never been explored. For example, it was only in mid-2017 that information was developed on the rate of healthcare utilization by autistics and it was found that their need for psychiatric care as well as care for the high incidence of autism associated comorbidities was far beyond that of the general population or other elements of the psychiatric patient population [9]. Similarly, it was not until September of 2017 that the rate of school suspension and expulsion was dramatically higher in the autistic population, and growing as the autistic population grew in numbers [10].

Recently, attention has been brought to bear on autism associated mortality rates. Although autism is not typically considered to be a fatal disease, several investigators have reported a significantly increased mortality in the autistic population with the major cause of death being suicide. A matched case cohort study based upon the Swedish National Patient Registry and the Cause of Death Registry looked at deaths between 1987 and 2009 and found a 256% greater death rate in autistic patients compared to the general population. The mean age at the time of death was 70.2 years for the general population and 58.39 for patients with autism, with suicide associated with better performing patients [11]. A review of 1706 children and adolescents reported an 18% increased risk of suicidal ideation or attempts in autism [12]. 35% of patients with Asperger’s syndrome were reported in a Canadian study t have attempted suicide [13]. Similarly, in Japan [14], Australia [15], England [16], and Belgium [17]. In a French review of the PubMed literature it was found that overall 21.3% of autism patients reported suicidal ideation or had attempted suicide, with the noteworthy observation that “... the methods used are often violent” [18].

Autism is quite heterogenous and has a broad pallet of potential symptoms. These symptoms transcend established investigative disciplines including behavioral studies, developmental studies, neurology, pharmacology and so forth. No truly workable definition of autism has yet emerged to define this heterogenous constellation of symptoms. Theories regarding the causes of autism include impairments within the autonomic nervous system [19], cerebellar dysfunction [20], mitochondrial impairment [21], exposure to toxins [22], and many others.

2. Autonomic function and autism

The autonomic nervous system has been implicated in symptoms that resemble those seen in autism. ASD has been associated with abnormal findings in autonomic related structures including the insula [23, 24] and the amygdala [25–27]. Autonomic related changes such as increases in basal heart rate [28–31] and diminished heart rate variability due to psychosocial challenges [32, 33] are seen in autism. The autism-autonomic linkage is exemplified by the consequences of respiratory sinus arrhythmia (RSA) that includes difficulties with socialization [30, 34], language difficulties [34, 35], and delays in cognitive development [35].

Kushki [19] hypothesized a chronically over activated autonomic system is a correlate of autism based upon the exaggerated levels of anxiety that attend autism [33], physiologic hyperarousal [36–38], and other correlates. Anxiety is perhaps the greatest co-morbidity associated with autism which may drive other features of the disease [39, 40], and has been associated with central nervous system structures that are linked to autonomic function [41, 42]. Phenotypically autism and anxiety both present with stereotyped repetitive and limited interests, avoidance behaviors and speech problems [43–45]. The relationship between anxiety and reported autonomic symptoms of elevated heart rate, perspiration, and other sequelae of the “fight or flight” reaction reveal a role for the peripheral nervous system function in autism [36–38]. However, this may be secondary to central autonomic activation. Central functions may manifest as elevated emotional responsiveness and exaggerated threat perception or diminished inhibition of fear responses [36], which are associated with the central structures mentioned above in which autonomic responsiveness and emotional responsiveness overlap.

There is a considerable body of evidence, which will not be reviewed here, that associates autism with cholinergic function in the central nervous system, specifically with various α -subtype nicotinic receptors, notably in the cerebellum. However, as autonomic function is classically considered to be a balance of cholinergic and catecholaminergic systems, perceived increases or decreases in cholinergic function may be manifestations of change in the dynamic balance of these systems with catecholaminergic tone. It may be possible to effect therapeutic change through manipulation of either acetylcholine-based manipulations or the counterbalancing of dopamine, norepinephrine, or epinephrine mediated mechanisms.

3. Adrenergic CNS changes in autism

Recent work by Hamilton, et al. [46] who sequenced exomes of families with a history of autism found deficiencies in the human dopamine transporter gene (hDAT), a protein responsible for the presynaptic reuptake of dopamine. CNS dopamine is a crucial element in systems that mediate motor function, motivation, attention and reward [47–50]. As this system is known to be associated with ADHD, and approximately 45% of autistic patients manifest symptoms of ADHD [3, 51–53], there is reasons to suspect a common pathway underlying these two diseases. Moreover, dopamine related genes *DRD1*, *DRD3* and *DRD4* are associated with an increased risk for ASD [54] as well as repetitive stereotyped behavior [55–57], and defiant and anxiety disorders [56]. Males with multiple tandem repeats in the monoamine oxidase-A (MAOA) promotor gene responsible for degrading dopamine show in increased proclivity for autism [58]. Aside from changes in synaptic dopamine uptake and degradation, changes dopamine receptor function and avidity have been reported [59–61], as have changes in dopamine synthesis and DOPA decarboxylase. Additionally, it has been observed that pharmacologic

manipulation of dopamine has clinical efficacy in ASD [62, 63], for example with risperidone, a drug approved to treat ASD.

Other lines of support come from observations of lower levels of dopamine β -hydroxylase in the plasma of autistic patients [64, 65] and reductions in platelet [66] and urine dopamine [67]. Similarly, inferences have been published that the mesolimbic cortex and striatum may provide a neurologic substrate linked with the motor and behavioral symptoms seen in autism as a result of a dopaminergic imbalance in these structures [68, 69].

Nguyen et al. [70] used *in silico* methods to clarify the genetics underlying the contribution of dopamine to the etiology and pathogenesis of autism and found genes implicated that regulate both Ca^{++} metabolism and dopaminergic neurotransmission. They found proteins implicated in ASD regulate dopamine signaling in multiple places including reuptake and catabolism, and they defined discrete molecular clusters that act on systems implicit in dopaminergic systems such as androgen receptors that stimulate DOPA decarboxylase. Another finding was the potential role of dopamine mediating the modulation of dendritic spines which determine synaptic strength and may be important in the developmental delays associated with ASD [71].

In an interesting cybernetic model, Kriete and Noelle [72] developed a sophisticated methodology to investigate the role of dopamine and the changes in executive function associated with autism. They showed that the intensely focused cognition associated with autism, as well as the pathognomonic lack of cognitive plasticity and inability to react with appropriate conscious focus to changes in the stimulus milieu could be modeled as changes in dopaminergic systems in the prefrontal cortex. By differentiating cognitive control from plasticity, and further by showing how developmental changes in younger brains can account for the timing of the manifestation of autistic symptoms, these authors' findings support a causal adrenergic mechanism underlying at least some of the symptoms associated with autism.

Taken together, a good case can be made for dopamine as a key mediator of the motor, speech, social behavior, behavioral perseveration, and reward aberrations that are typical symptoms of autism. The precise regulation of dopaminergic function of autonomic function appears to involve the projection of Purkinje cells to the medial prefrontal cortex (mPFC) and the ventral tegmental area (VTA) of the striatum. Atrophied Purkinje cells is one of the most consistent neuropathologies associated with autism [73–76], and MRI data indicates persons with autism have smaller than normal cerebellar vermal volume [77]. Mice with diminished Purkinje cell mass evidence numerous autistic symptoms such as repetitive behaviors and impaired executive function [78]. Cerebellar Purkinje cells project to the mPFC where it appears they modulate dopaminergic transmission in this region directly, and via a remodeling of the VMA and thalamic interactions with the mPFC, and it has been suggested that cerebellar deficits observed in autism result in cortical, thalamic, and striatal integration via dopamine mediated pathways [79].

An immunologic linkage of dopaminergic function in autism was reported by Kirsten et al. [80] when they prenatally exposed rat pups to lipopolysaccharide, a stimulator of innate and adaptive immunity. Autistic symptoms of impaired communication, deficits in learning and memory, and repetitive/restricted behavior were observed in the presence of impaired tyrosine hydroxylase (TH) function which was taken as a marker of reduced striatal dopaminergic function. Support for this concept was also found when rat pups were given poly I:C, an immunogenic stimulator, and upregulation of various genes associated with dopamine neural development were observed [81].

The phosphatase and tensin homolog on chromosome ten (PTEN) is a tumor inhibitory gene that inhibits PI3K and MAPK pathways, and a germline mutation of

this gene has been associated with autism [82]. Mouse mutations of this gene have resulted in symptoms similar to autism [83], and PTEN deletions have been found to enhance the survival and the function of dopaminergic neurons [84]. Work in this area has shown that mice with PTEN mutations have elevated TH and DA2 receptors in the striatum and prefrontal cortex, that PTEN reduces TH phosphorylation via MAPK suppression, downregulates dopamine synthesis in PC12 (pheochromocytoma) cell cultures, and that a PTEN-TH pathway may function as a “core regulator of dopamine signaling”. Moreover, this mechanism appears to be operative in autistic patients, as 3 PTEN mutants identified in autistic patients cannot suppress TH, which supports the concept of TH suppression as a potential mechanism for therapeutic intervention in autism [85].

Consistent with the finding that TH over activity might underlie the symptoms of autism is the finding by D’Souza et al. [86] that the commonly used model for autism in which symptoms in animals are induced by administering valproic acid is related to the ability of this agent to induce TH transcription at every concentration tested.

4. GI abnormalities in ASD

Autism is associated with gastrointestinal pathology from the esophagus to the colon [87–91]. The literature suggests that GI pathophysiology is an intrinsic component of autism in many patients and may be a central component to the etiology of the disease. GI problems have been reported in 42% of children with ASD and 12% of controls, with chronic diarrhea and constipation being the most prevalent problems. The severity of these problems correlates with the severity of ASD [92]. It is noteworthy that in both GI dysfunction and ASD imaging reveals abnormalities in brain regions associated with emotional and sensory functions [93, 94], and GI problems contribute to behavioral problems, attentional deficits, and self injury [95]. Gut bacteria influence intestinal permeability, mucosal immunity, the enteric nervous system, pituitary functions, and the modulation of pain (cited [96]).

There is increasing reason to believe that the interaction between gastric microbiota and the brain are contributory to the symptoms seen in ASD. This is mediated via the autonomic innervation of the intestine and the hypothalamic–pituitary axis which is innervated by catecholamines and which generates GI signaling molecules affecting enteroendocrine and mucosal immune cells. The “Gut Brain Axis” is comprised of central and peripheral nervous systems as well as the neuroendocrine and immune systems, and communication is bidirectional, with vagal inputs to the brain as well as endocrine and neuroendocrine signaling [97]. Catecholamines are associated with stress reactions and, interestingly, GI microbiota respond to stress with changes in their efferent and afferent catecholamine responses (reviewed in [98]).

A trial of 36 autistic children found pain, chronic diarrhea, bloating, GI irritability, chronic gastritis, esophagitis, chronic duodenitis, diminished carbohydrate digestive enzymes and reduced pancreatic exocrine secretion in response to secretin challenge [88]. Secretin has not been found to be an effective treatment for autism. In a survey of parents of 500 autistic children, half responded that their children had loose stools or chronic diarrhea, and intolerance for wheat and cow’s milk [99]. A number of reports mention improvements in autistic symptoms when reduced gluten and casein diets are implemented and the return of symptoms when these diets are terminated (cited in [100]).

Lucarelli et al. [101] observed an improvement in social skills and the ability to communicate in a trial of 36 autistics who were given diets with diminished

gluten and/or cow's milk, with improvements observed in 5 of 7 objective behavioral scales. Similar findings have been reported by others [102–105]. Following one year on this diet symptoms returned upon termination of the dietary restrictions [104]. Intestinal permeability was found increased to lactose in a number of high functioning autistic children compared to age matched controls, with no increased permeability to mannitol, which was interpreted to mean a diminution in the tight junctions of gut epithelium [106] and the subsequent release of incomplete gluten and casein digestive products. Autistic patients reportedly manifest significantly higher levels of IgA for casein, gluten, lactalbumin and β -lactoglobulin [101, 107].

These observations give rise to the Leaky Gut Hypothesis of Autism, which states that various digestion products can enter the blood through leaky tight junctions in the gut and interact with the immune and central nervous systems in ways that facilitate the onset of autism. Gut peptidases release short chain peptides called exorphins that have structural similarity to endorphins. Gliadomorphins and casomorphins are stable examples of these peptides that are known to induce psychosis [108]. β -Casomorphin-7 is elevated in the urine of autistic patients [104], and when infused into the blood stream of rats has been shown to activate the transcription of the gene *c-Fos* in the brain [109]. However, dietary restrictions do not cure autism.

While controversial, elevated short chain fatty acids (SCFA) have been associated with autism [110], and both central and peripheral administration of propionic acid (PPA) to rats induces ASD-like impairments that include aberrant motor movements, stereotyped repetition, EEG changes, cognitive deficits, perseveration and social impairment, as well as increased oxidative stress, glutathione depletion, neuro-inflammation, altered lipid profiles and more [111]. SCFA are digestive products derived from fiber and protein. The most common SCFA include propionic PPA and butyric acid (BA) [112]. BA and PPA are metabolized in the liver via the portal circulation, however areas of the distal colon are outside of the portal circulatory bed, and the systemic effects of BA and PPA are believed to be significantly underestimated [110, 112]. SCFA, including PPA, activate G protein coupled neural, effect neurotransmitter synthesis and release, and mediate such diverse events in the nervous system as Ca^{++} gating, mitochondrial function, lipid metabolism, immune function, gene expression and the role of tight junctions [110]. SCFA are believed to modify the activity of TH, and there are 3 ways in which the SCFA BA modifies TH activity: (1) modulation of transcription via chromaffin remodeling, (2) activation of various transcription mediators, and (3) by interfering with TH mRNA [113–116]. Subsequent work by Nankova, et al. [117] have shown that PPA elevates TH mRNA levels and that SCFA increase TH and subsequent catecholamine synthesis.

This dietary model allows for the elevation of cortical and striatal dopamine activity via elevated TH synthesis and activation, and which has been invoked as a potential mechanism for the actions of risperidone [118, 119], one of the two drugs approved for the treatment of the irritability associated with autism. It is worth noting in this context that PPA is structurally similar to valproic acid (VA), and has similar effects to VA, which is a treatment known to induce autistic symptoms, and used as a model for this purpose [120–122]. As cited above, VA appears to induce ASD-like symptoms by stimulating TH transcription in a manner similar to butyrate [86].

It is worth noting that relative to the participation of gastrointestinal events which may underlie autism, recent developments in the study of the human biome and investigations into GI function have revealed that the gut is the source of a number of neurotransmitters and neurotrophic factors, thus opening a previously

understudied source of pharmacologic agents which may regulate CNS function. *E. coli* and *Clostridium* sp. have been shown to elevate free GI catecholamines and dopamine increases colonic water absorption [123]. GI microbiota produce catecholamines and recognize them in the environment [124–126]. Epinephrine and norepinephrine are implicated in the virulence, ability to adhere, and chemotactic properties of luminal bacteria [127].

In the work discussed above, it is important to note that PPA activates peroxisome proliferator-activated receptor gamma (PPAR- γ), and that this orphan receptor has been shown to have independent effects on the mediation of catecholamine and opioid pathways by SCFA [128], and that, as discussed below, PPAR is considered to be a “master regulator” of lipid homeostasis both centrally and peripherally. This later finding plays into the growing literature of lipid metabolism dysregulation in autism. PPAR also has immunologic functions that have been found to be related to metabolic and neurologic pathologies [129].

5. Dopamine underlies autistic symptoms in the gut and the CNS

Any comprehensive approach to the treatment of autism must accommodate many different organ systems, certainly the gut and the CNS. As discussed above, the neurotransmitter function of dopamine is well known, including its modulatory effects on motor function, mood, emotion, irritability, reward, and other systems which are affected by autism. However, there also exists in the mesentery a paracrine dopaminergic system that regulates the secretion of bicarbonate [130], the secretion of digestive enzymes by the exocrine pancreas [131], and which controls sodium transport in the lower intestine [132]. Dopamine also has documented effects on gut motility and mucosal blood flow [133–135]. As early as 1994 elevated blood levels of levels of dopamine have been associated with autism [136]. It is known that ASD is associated with elevated levels of dopamine in the tracts linking the amygdala and prefrontal cortex in children with ASD [137, 138].

What is less known is that approximately 42–46% of the dopamine in the body is produced in the gut. Eisenhower and colleagues at NIH [139] studied 8 patients undergoing elective abdominal surgery and 47 patients who underwent cardiac catheterization. Tissue samples from the stomach and duodenum were obtained and compared, as were arteriovenous concentration differences and rates of renal clearance of dopamine and its metabolites in conditions of different sympathetic nervous backgrounds for dopamine not converted to norepinephrine. They found considerable dopamine synthesis in the stomach, pancreas, and duodenum, with renal elimination of dopamine and its metabolites. Dopamine has a natriuretic function in the kidney; however, there was significant overflow of dopamine into the renal venous circulation that allows for systemic effects. As expected, cells in the stomach, pancreas, and duodenum stained positive for TH. The authors could not account for the amount of dopamine added to the mesenteric venous circulation, as it cannot be explained by sympathetic activity or diet, and their results were consistent with findings in swine [140].

In keeping with the concepts presented herein, it is relevant that in the liver, bile salt production and release are also under the control of dopamine [141, 142]. Bile salts are known to occur not only in the periphery, but in the CNS as well, where they appear to contribute to neurologic decline and blood brain barrier permeability [143, 144]. Bile acids are the predominant steroid in the brain, with levels that are 10x greater than those found in the blood indicating local synthesis, and with higher titers than that of pregnanolone, which was once considered the predominant neurosteroid [145].

In the brain, it has been observed that chenodeoxycholic acid or deoxycholic acid induce the phosphorylation of occludin and increase the permeability of tight junctions via an Rac-1 dependent mechanism [146], making it conceivable that tight junctions in the gut are similarly effected by bile salts under the control of dopamine. It is well known that bile salts upregulate the orphan X receptors Farnesoid X Receptor (FXR), Liver X Receptor (LXR), Retinoid X Receptor (RXR) and PPAR. These nuclear receptors regulate the metabolism and homeostasis of glucose and lipids in numerous ways, including the transcription of the genes that regulate energy metabolism. Beyond the role of lipids in cell membranes and myelin sheaths, there is a growing body of literature to support the concept that lipids play a crucial signaling and regulatory role in cognition and other CNS events. This would appear to be significant as the brain comprised fundamentally of lipid and has the highest rate of glucose utilization in the body.

While it is commonly stated that autism occurs more frequently in males, at a rate of 4 boys for each girl [147], it is less commonly known that in severe autism this ratio increases to 11 to 1 [148]. Numerous sexual dimorphisms in the brain have been described (reviewed in [149]), such as brain size, hemispheric communications, differential gene expression, and more. It is worth noting that there is a growing body of literature implicating dopamine modulation of behavior as part of these sexual dimorphisms. One mechanism which may underlie the sexual dimorphism seen in the expression of ASD may relate to *SRY*, the sex-determining region on the Y chromosome, which is responsible for many male traits, including the differentiation of bipotential embryonic gonads to become testes. *SRY* is an intronless gene that co-localizes with dopaminergic neurons in the hypothalamus, frontal and temporal cortex, striatum, ventral tegmental area (VTA), locus coeruleus and substantia nigra. In humans, *SRY* expression is found in a population of TH positive neurons in the VTA, which is the origin of the dopaminergic cell bodies of the mesocorticolimbic dopamine system which is widely implicated in the drug and natural reward circuitry of the brain. It is important in cognition, motivation, orgasm, drug addiction, intense emotions relating to love, and several psychiatric disorders. *SRY* has been found to regulate the transcription of TH via the AP-1 binding site on the TH promoter. The synthesis of MAO-A, an enzyme which inactivates DA, and which has polymorphisms associated with the severity of ASD, is also mediated by *SRY* in a manner that elevates extracellular dopamine. Thus, *SRY* appears to be expressed in regions of the brain, and have pharmacologic activity on dopaminergic function, in a manner that is consistent with the preponderance of ASD in males that is pathognomic for this syndrome (reviewed in [149]).

Consistent with the increased prevalence of ASD in males, work in a mouse model has shown that a 16p11.2 gene deletion, which is associated with autism, affects the striatal reward system. While both sexes had 50% reductions in mRNA associated with ERK1, an important signaling kinase, in males there was an increase in ERK1 activation at baseline and in response to sugar in a manner associated with reduced striatal plasticity not shown in females. These changes were associated with an overexpression of dopamine D2 receptors in the striatum [150].

A mechanism by which sleep disturbances associated with ASD may be mediated involves the striatum, an area known to coordinate reward, learning and cognitive behaviors [151, 152] as well as to modulate circadian locomotor and retinal responses [153, 154]. This locus has been shown to be responsible for the maintenance of normal circadian rhythm functionality, and this system appears to be controlled by dopamine. Activation of D₂ receptors has been found to regulate clock genes in the striatum, controlling circadian events. Hood et al. [155] found that depletion of striatal dopamine by various methods, including the use of

AMPT, blunts normal circadian functions and that daily dopaminergic activation is required to maintain normal circadian rhythmicity.

In the context of a dopamine mediated model of autism, it is interesting to note that bile acids under catecholamine control inhibit the GABA_A receptor [156, 157] in a manner that that diminished GABA related inhibitory post synaptic potentials. Inhibition was observed to occur in a stereospecific receptor-ligated, ion channel dependent manner, independent of lipophilicity, and consistent with the behavior of other known GABA receptor blockers. Interestingly, the inhibitory potencies of various bile salts corresponded best with their binding constants with albumin.

Taken together there is evidence for a dopaminergic system which might underlay and unite the symptoms of autism which manifest as central nervous system changes in mood, attention, cognition, socialization, etc., and those seen in the gut as changes in secretory, digestive and excretory functions.

6. The role of energy metabolism

ASD and energy metabolism are associated in several ways beyond the gut with glucose and lipid metabolism affected. Key among them is the role of bile salts under the control of catecholamines. Bile regulates FXR, LXR, and PPAR which are involved in the regulation of glucose metabolism, insulin sensitivity, lipid signaling and homeostasis. As a class, these ligand-inducible receptors are upregulated in the presence of their ligand, such as bile salts, and after binding they migrate to the nucleus where they exert genomic and epigenomic effects upon transcription and translation of the genes that mediate glucose and lipid utilization (for reviews see: [158–165]).

Diabetes and metabolic syndrome are recognized comorbidities of ASD [154]. Catecholamines regulate bile acid release and the FXR upregulates the synthesis and secretion of bile salts from the gall bladder by stimulating the bile salt efflux pump in order to provide bile to solubilize fat soluble nutrients and vitamins from the gut and may have a similarly stimulate FXR in the brain. In mice, FXR deficiency leads to insulin resistance and reduced glucose tolerance [163, 166, 167], and the finding of FXR in pancreatic islet cells that affects insulin release allows for a regulatory role of local bile acid concentrations in insulin release and glucose tolerance [168, 169]. In the CNS, it is commonly known that the influence glucose receptors in the hypothalamus, carotid bodies, and other sites summate to mediate the central nervous control of glucose metabolism. Eating, satiety and similar energy mediated events in the brain are known to be modulated by the sympathetic nervous system, predominantly by dopaminergic systems [170]. Sympathetic afferents from the hypothalamus and other central site, under the control of various agents such as catecholamines and leptin are known to regulate glucose synthesis, insulin sensitivity and similar events (reviewed in [171–174]). Severing the autonomic projections to the islets of Langerhans resulted in a 75–90% impairment in the ability to regulate serum glucose in response to insulin induced hypoglycemia [175]. Although the effects of catecholamines on lipid homeostasis have been defined in the gut, these mechanism can also serve as a model in brain tissue, since this organ contains 25% of the body's cholesterol but only 2% of its mass [176], and most of the lipid synthesis and metabolism in the brain occurs *de novo* within the CNS.

There exists a growing body of work that lipid metabolism underlies cognitive function. Accumulating evidence supports the idea that HDL and the mechanisms that regulate lipid metabolism also influence neurodegenerative diseases including autism, amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, and others [177]. Just as HDL have a demonstrably cardio-protective role, they

also appear to have a neuro-protective role. HDL are made throughout the body and serve to remove excess cholesterol from peripheral tissues for excretion in the bile and for steroidogenesis. In a study of 139 centenarians it was found that plasma HDL correlated with mental acuity in age [178]. This was confirmed in another study of 159 centenarians [179], again in a longitudinal population study in Amsterdam [180], and supported by the finding that low HDL was associated with intellectual impairment in age [181–183]. Effectors like cholesteryl ester transfer protein (CETP), which increase HDL are similarly associated with durable cognitive function in later age [179, 184, 185].

Bile salts can be released inappropriately via a “leaky gut” syndrome that ASD or they can be made locally in the brain under the control of catecholamines. Their synthesis and biologic functions have been described in a variety of non-gastric tissues, including the brain. As reviewed by Quinn and DE Marrow [186], bile acids and their salts are now viewed as steroid hormones, and not merely as detergents that solubilize lipids. Consistent with their role as the predominant brain steroid [145], in the rat that the primary bile acid chenodeoxycholic acid composed 95% of brains bile acid. Further, the most abundant oxysterols found in the CNS are the C₂₂ and C₂₆ intermediates of bile acid synthesis.

One of the agents that regulates HDL homeostasis is the LXR, which is upregulated in the presence of the bile salts that solubilize and accompany plasma and tissue lipids. LXR is a cholesterol sensing and regulating molecule and cholesterol functionality is necessary for healthy cell membrane function, which is crucial to synaptic function. LXR has been demonstrated to improve cognitive performance in animal models of Alzheimer’s disease presumably via the induction of HDL [cited: [177]].

Once believed to be the master regulator of glucose and lipid metabolism, PPAR- γ is associated with the maturation and development of adipocytes, the deposition of lipids, glucose metabolism, insulin sensitivity and other related events [187]. PPAR- γ has been shown to be mediated by bile salts and dopamine via phospholipase C in a calcium dependent manner, with elevations in dopamine resulting in increased PPAR- γ in cardiac myocytes [188]. PPAR- α is abundantly expressed in skeletal muscle, liver and brain [189, 190], and is associated with dyslipidemia, a condition often seen in autistic patients [190–193]. PPAR- α has been associated in the literature with central dopaminergic function as it appears to influence the activity of antipsychotic agents known to interact with dopaminergic neurologic systems [194, 195]. It has also been implicated in reduced GABAergic interneuron firing in pyramidal neurons resulting in cortical excitation [196–199]. D’Agastino et al. [200] have shown that central nervous system reduction in this “Master Regulator of Lipid Homeostasis” is associated with autistic like behaviors that include; repetitive and perseverative behaviors, loss of cognitive flexibility and reduced spatial information processing. They documented PPAR- α deprivation resulted in resistance to central glutamate stimulation via NMDA receptors, reduced GABAergic interneurons in the frontal cortex and hippocampus with dystrophic neurons in these structures, and increased gamma waves with decreased theta wave frequency.

Historically, there is a well-defined relationship between stress, catecholamines, and plasma lipids (reviewed in [25]). Stress, which is characterized by elevated levels of circulating catecholamines, is associated with increased plasma lipids, reduced glycemic control, diminished insulin secretion and insulin insensitivity, all of which can be associated with ASD. This is consistent with the aggressive fighting responses associated with catecholamines significantly elevating NGF in sympathetic ganglia and in the absence of ACTH or corticoids [201]. Various central mechanisms have been implicated in these events, including, the ventromedial

nucleus of the hypothalamus and hippocampal efferents to the hypothalamus. These central nervous system events can be translated into hyperlipidemia in three ways: via adrenal epinephrine release, via elevated pancreatic glucagon secretion, and via the regulation of hepatic glycolysis and gluconeogenesis. All three of these pathways are regulated by the sympathetic nervous system.

These findings fit with an emerging metabolic model of autism in which CNS control of energy metabolism and the autonomic nervous system as an integrating modality that senses and regulates those changes in the periphery and modifies these effects centrally. Integration of reward, satiety, insulin release and sensitivity, related endocrine events, as well as circadian clock mechanisms and similar systems which are impaired in autism appear to be mediated largely in the hypothalamus and brain stem via various nutrient sensing mechanisms which reticulate throughout the CNS to the cortex, basal ganglia, pyramids and so forth. (for a review see [202]). Cholesterol, LXR, PPARs and other agents which are known to regulate energy metabolism in the periphery appear to do so in the CNS as well and these mechanisms map well to the deficiencies seen in autism. It is particularly noteworthy that many of the events mediated by the nuclear receptors LXR and PPAR are cell and ligand specific, and that changes in cholesterol metabolism can have profound changes on membranes and their functions. That these changes can vary as a function of cell type provides a mechanism by which metabolic impairments in discrete brain regions may occur in ways that compromise specific nuclei and tracts.

Taken together, there appears to be linkage between catecholamine metabolism both centrally and peripherally, the regulation of energy homeostasis, and central nervous system function in a variety of pathologic states. There is a growing body of evidence to indicate a relationship between central and peripheral nervous system regulation of glucose and energy homeostasis, and abnormal cognitive function, as exemplified in autism.

7. Nerve growth factors

Nerve growth factor (NGF) in the brain is stimulated by catecholamine synthesis [203] and regulates the morphology of the catecholamine synapse. Neurotropic NGF is required for catecholaminergic neuron survival and differentiation. It is released into the synapse with catecholamines and it determines the synaptic architecture with elevated levels of NGF resulting in elevated levels of TH, catecholamine synthesis and synaptic neurotransmission [204–206] since NGF concentrations have a direct effect on the budding and arborization of catecholamine dendrites [207, 208] as well as the density of target tissue innervation [209, 210]. Similarly, elevated catecholaminergic transmission is associated in a dose dependent manner with brain derived nerve growth factor (BDNF) in a pre-synaptic manner [211]. This is consistent with the finding that the loss of a Brain Derived Nerve Growth Factor (BDNF) allele in a mouse knockout model prevented the loss of sympathetic islet innervation in an immune based diabetic model [212].

NGF has a hyperplastic, hypertrophic effect on catecholaminergic neurons characterized by elevated TH [213–215] that results from binding to its tyrosine kinase receptor TrkA expressed on the axons of catecholaminergic neurons [216]. In this way pre-synaptic release of neurotransmitters exerts a differentiating effect post-synaptically to mediate catecholamine synaptic architecture, the number of neurons, and innervation density [207, 217].

NGF is known to increase with increased catecholaminergic nerve traffic and with stress [218], and results in the sprouting of new nerve fibers in the stellate ganglion and elsewhere in the sympathetic nervous system [219, 220]. NGF and

BDNF are important mediators of neurologic function in the brain with the ability to mediate short and long term neurologic function in areas associated with ASD like the cortex and hippocampus [221, 222]. NGF has been shown to promote sympathetic neural growth, differentiation and to enhance target innervation [205, 208–210, 223, 224] and NGF is known to be elevated in PTSD [225–227], a disease with a similar constellation of symptoms to autism. NGF leads to sympathetic sprouting and supports dendritic geometry of the newly sprouted nerve terminals for the life of the sympathetic neural substrate [228, 229]. NGF is known to effect memory directly [230], indirectly [220, 231, 232], and through its actions on NE, as well as indirectly via hypothalamically mediated release of cortisol [233].

8. L1-79

L1:79 is D,L α -methyl-para-tyrosine, abbreviated AMPT. It inhibits the activity of TH, which catalyzes the first transformation in catecholamine biosynthesis, i.e., the conversion of tyrosine to dihydroxyphenylalanine (DOPA) which is the rate limiting step in catecholamine synthesis. L α -methyl-para-tyrosine was approved by the FDA in 1979, is marketed under the name Demser®, and is typically called metyrosine and abbreviated AMT.

α -methyl-para-tyrosine is a tyrosine analog that competes competitively for TH and is excreted mostly unchanged in the urine. Demser was approved for presurgical use in the treatment of pheochromocytoma, a catecholamine producing tumor which when manipulated surgically releases pathologic levels of catecholamines into the circulation that can result in serious AE. Demser minimizes this potentially serious complication and can treat pheochromocytoma patients who were not qualified for surgery. It is approved for use in doses between 1 and 4 g/day in divided doses. The doses of L1-79 used in autism clinical trials was 90 mg tid to 400 mg tid of which only 50% is the L-isomer.

While Demser is intended to deplete adrenal medullary catecholamines as fully as possible L1-79 is intended to reduce catecholaminergic tone slightly, a use for which Demser is inappropriate. The published half-life for Demser is 3.53 hours [234], whereas the half-life for L1-79 has been found to be between 10.3–14.3 hours [235]. This is presumed to result from a competitive inhibition between the dextro and levo forms of the molecule for the L-amino acid transport mechanisms in the body resulting in more time on target for the racemate. Since only 50% of L1-79 is the active L-isomer, and as it persists at the receptor for a longer duration, L1-79 is suitable for bid dosing and is much better tolerated at the lower doses used to get a therapeutic effect in ASD.

Adverse events associated with Demser include sedation that typically habituates but might persist at doses >2 g/d, temporary changes in sleep, extrapyramidal signs including tremor at high doses, trismus and parkinsonism at high doses, dose dependent confusion that resolves with dose reduction, dose related diarrhea, and infrequent AE that include crystalluria, nausea and vomiting, and impotence. None of these have been observed in autism except for 2 patients who manifest crystalluria without clinical consequence at the 200 mg tid dose.

It should be noted that D,L α -methyl-para-tyrosine as described herein for the treatment of autism is also used in a polytherapeutic regimen for the treatment of patients with late stage cancer (SM-88) under the Tyme Technologies Inc. at doses that are a fraction of the lowest approved dose for Demser, and has been well tolerated.

9. Preliminary clinical observations

In a proof of concept trial in 8 patients of both sexes between the ages of 2.75 to 24 years of age and without Rett or Fragile X syndrome. Doses began at doses of 90 mg tid and were escalated to 200 mg tid for most patients with two patients receiving a brief course at 400 mg tid, which was not found to increase efficacy. All doses were well tolerated. Patients were washed out of their legacy medications and 6 patients were maintained on L1-79 alone. Two patients were restarted on one of their legacy medications at lower than their pre-study dose. L1-79 in this study had a therapeutic effect on the core symptoms of autism as defined by the ABC-C (Figure 1), the CPRS (Figure 2), ADOS (Figure 3), and the CGI (Figure 4). This includes improvements in socialization, communication, repetitive movements, sleep disturbances, and other symptoms of ASD. Interestingly, the Autism Diagnostic Observation Schedule 2 (ADOS), which is the “gold standard” for quantifying the lifetime severity of ASD was profoundly influenced by L1-79 treatment. In the 6 patients in whom the ADOS was measured a mean decrease of 30% was observed with one patient experiencing a reduction of 47% (Figure 3) which took him below the threshold for a diagnosis of autism following 10 weeks of treatment, although

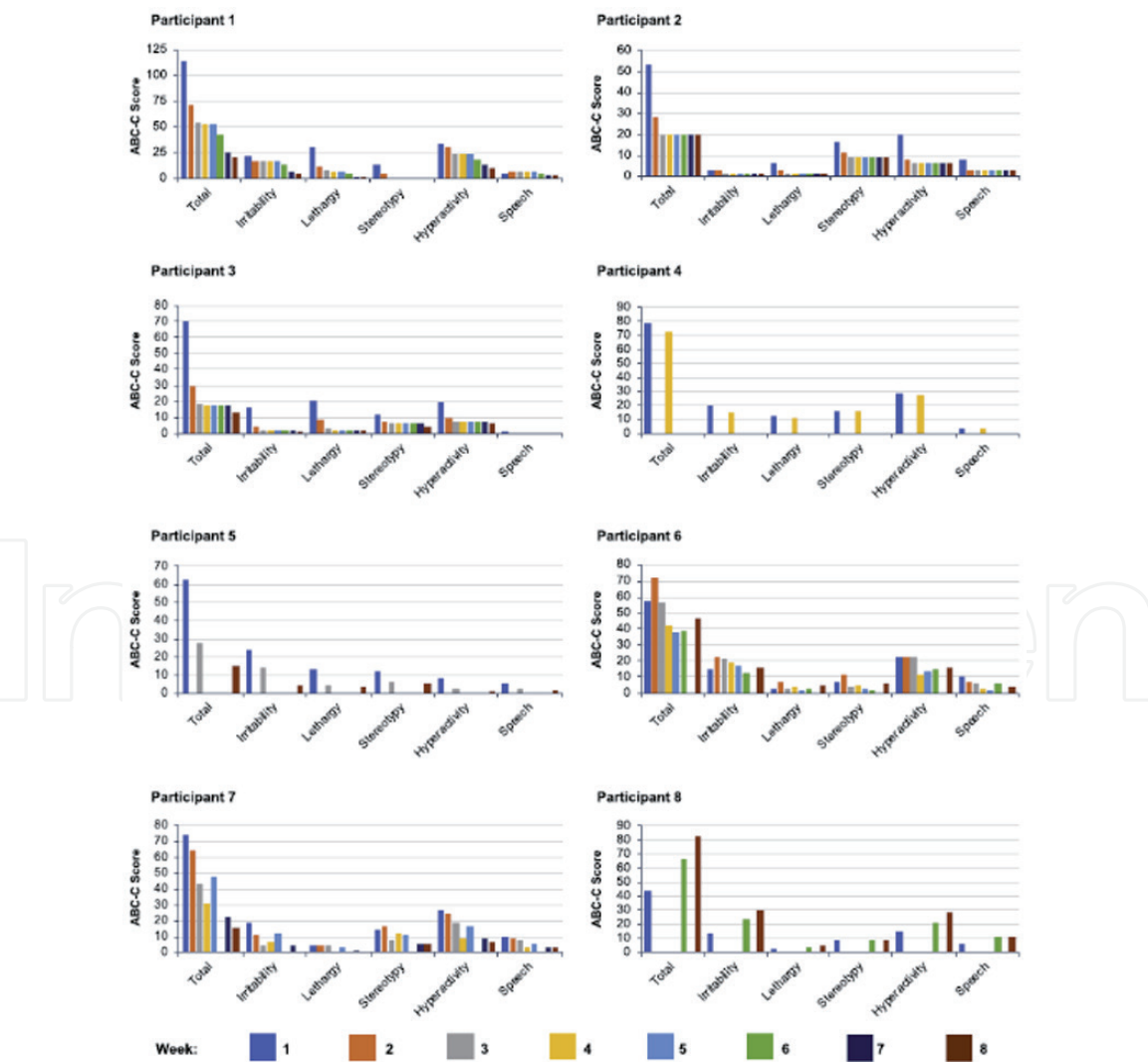


Figure 1.
Proof of concept study: Aberrant behavior checklist-community (ABC-C) scores. Domain scores for each participant during weeks 1 to 8. Because of participant-specific factors, ABC-C scores were not recorded at all visits for all participants.

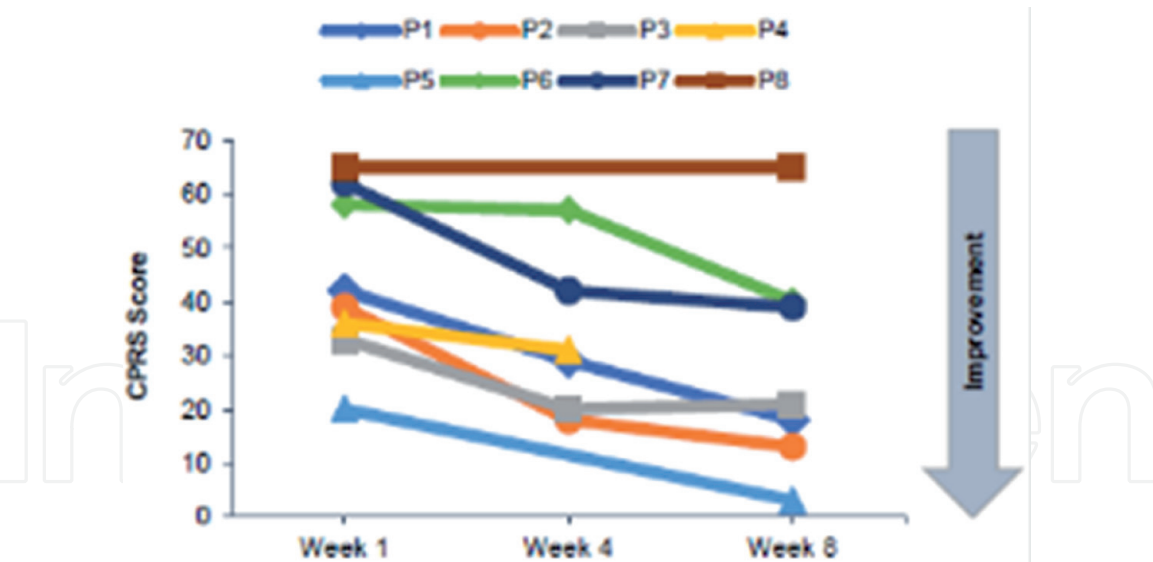


Figure 2.
Proof of concept study: Connor parent rating scale (CPRS) at 4-week intervals for 8 participants. Some participants did not have all assessments.

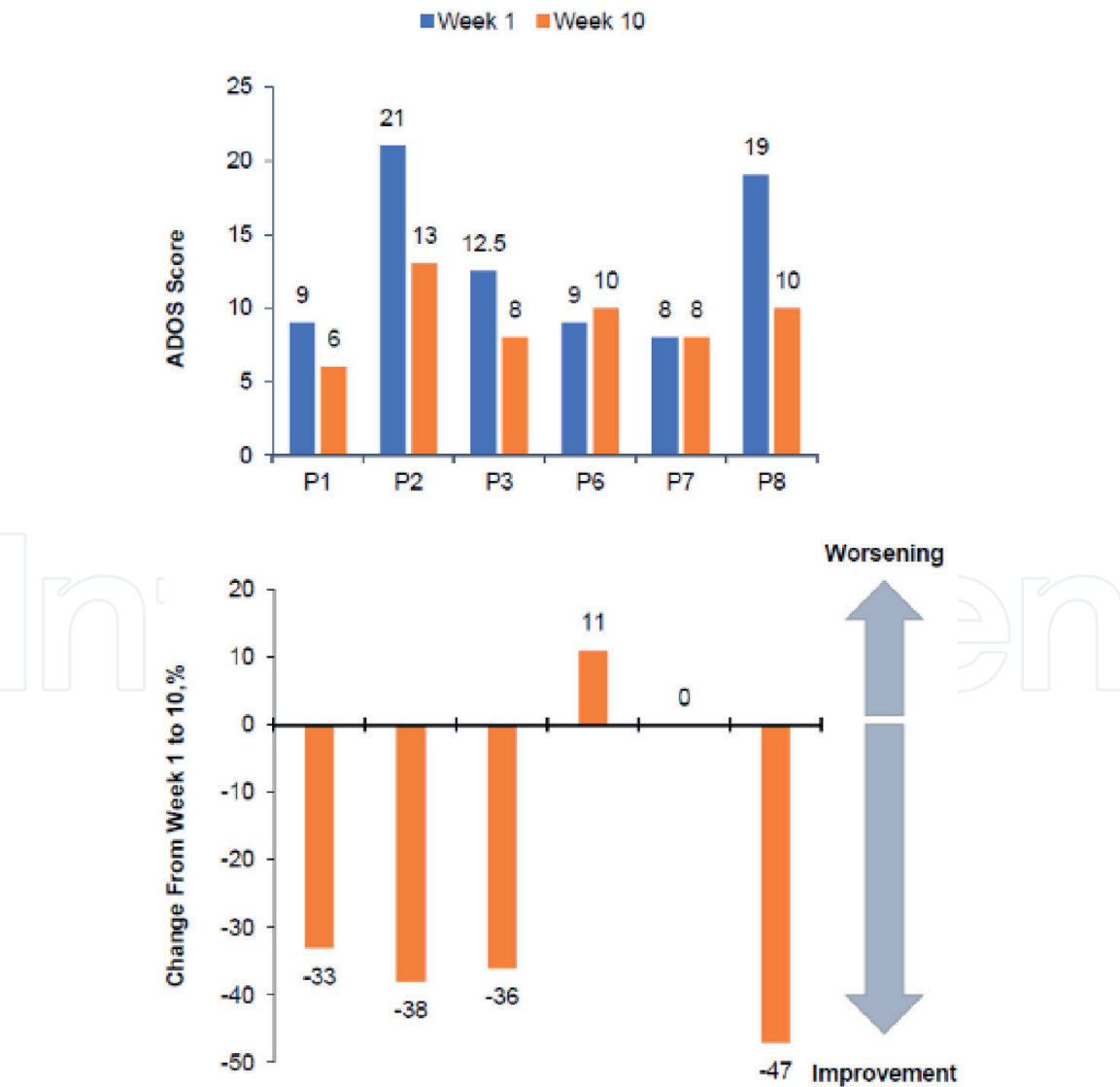


Figure 3.
Proof of concept study: Autism diagnostic observation schedule (ADOS) scores for the 6 participants tested at baseline and week 10.

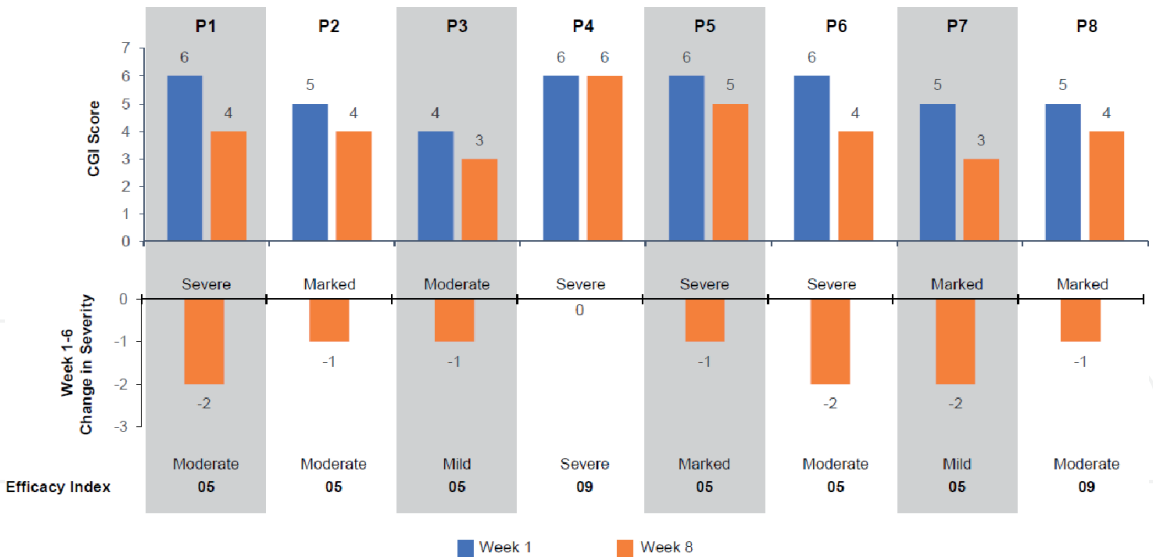


Figure 4.
Proof of concept study: Clinical global impressions (CGI) scores for 8 participants. Top panel shows absolute scores at week 1 and week 8. Bottom panel shows the change from week 1 to week 8. The qualitative interpretation at week 1 appears above each participant change in score, and the interpretation at week 8 is shown below each bar. Each participants efficacy index at week at appears at the bottom.

he was still on the spectrum [236]. As can be seen in the ABC-C scores, these effects were observed rapidly.

A follow-up randomized, double blind, placebo-controlled 28-day study of 39 patients has been completed and the results are currently in preparation for publication [237]. While 28 days was too short to demonstrate much of an effect, per the FDA the existing toxicology did not permit a longer treatment duration at that time. Participants were male patients between the ages of 13 and 21 years of age with a diagnosis of ASD based on DSM-5 criteria and confirmed by Autistic Diagnosis Interview-Revised (ADI-R), ADOS and expert clinical opinion, stable on no more than one concomitant medication with no planned changes in psychosocial interventions during the study and sufficiently tolerant and capable of complying with the requirements for this study. Results from this brief study can be seen for the CGI (**Figure 5**), Social Response Scale-2 (SRS) social motivation T scores (**Figure 6**), ADOS (**Figure 7**), Vinland Adaptive Behavior Scale-II (VABS) socialization standard score (**Figure 8**), and the SRS DSM-SCI T scores (**Figure 9**).

Anecdotally, numerous salutary behaviors were observed in these studies. Two teenage boys hugged and kissed their parents for the first time. One teenager with a history of self mutilating behavior stopped hurting himself. Subjective aspects of socialization such as empathy, effective communication, emotional expression, better sleep patterns, and engagement with peers were reported by parents and teachers and a school bus driver who were unaware of the trials.

The proof of concept study was conducted under the assumption that, per the 505(b)(2) guidelines, any stereoisomer of a drug is considered to be the same drug, and therefore the use of L1-79 was an unapproved use of an approved agent (Demser). In subsequent discussions with the FDA this was disallowed. The FDA required that the proof of concept study be discontinued and approved a follow-on pilot study that was limited to 28 days based upon the toxicology then in existence. It is noteworthy that when study drug was discontinued after the 28-day pilot study patients regressed to baseline within one week whereas the proof of concept patients who had been on study drug for as long as 6 months maintained some residual benefit following the discontinuation of medication.

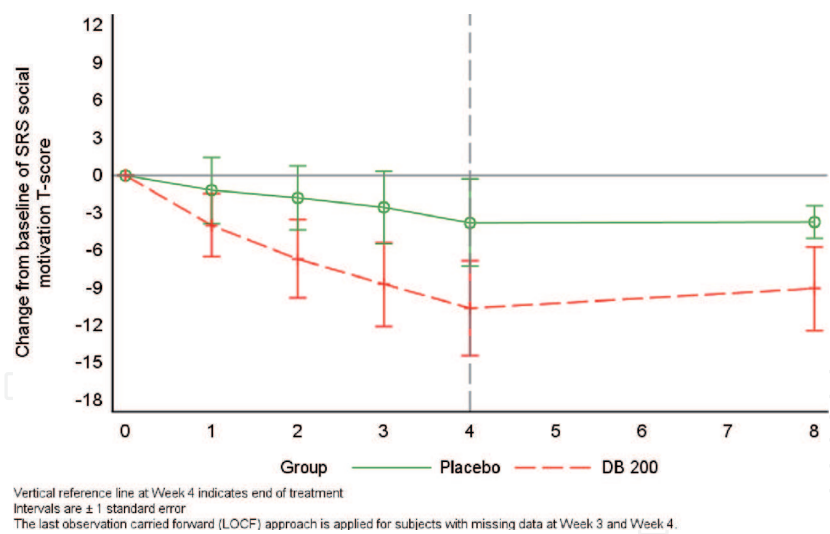


Figure 5.
Pilot study: Change in clinical global impression-severity (CGI-S) over time and individual patient responses from baseline to week 4. Upper panel is the change over time by study week for L1-79 200 mg and placebo. The lower panel is individual patient responses for L1-79 200 mg and placebo.

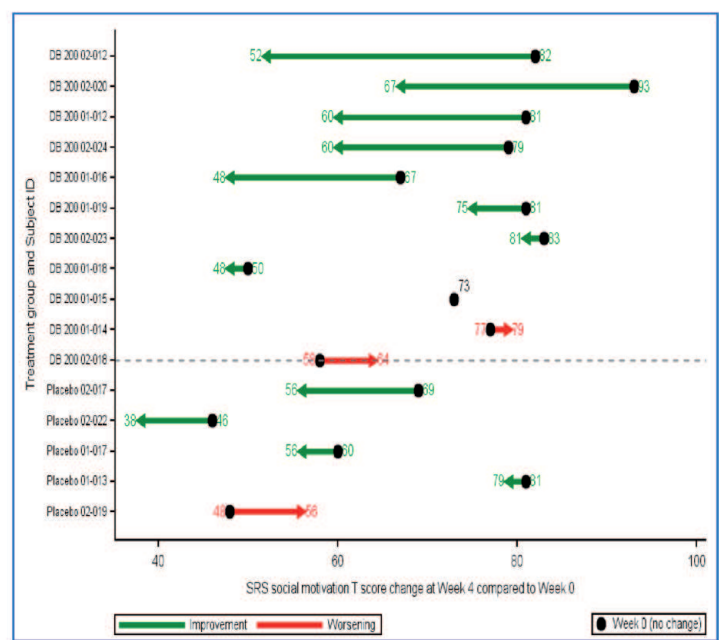
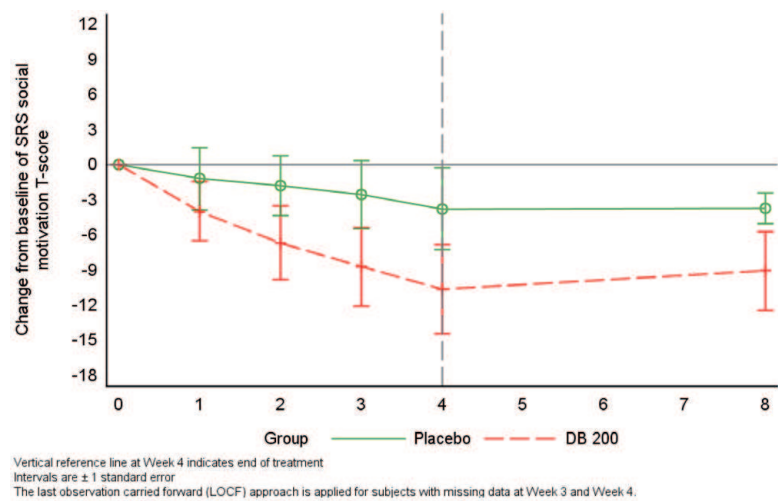


Figure 6.
Change from baseline over time and individual patient responses in the social responsiveness Scale-2 (SRS-2) social motivation T-score at week 4. Upper panel is change from baseline over time for L1-79 200 mg and placebo. Lower panel is individual changes for L1-79 200 mg and placebo.

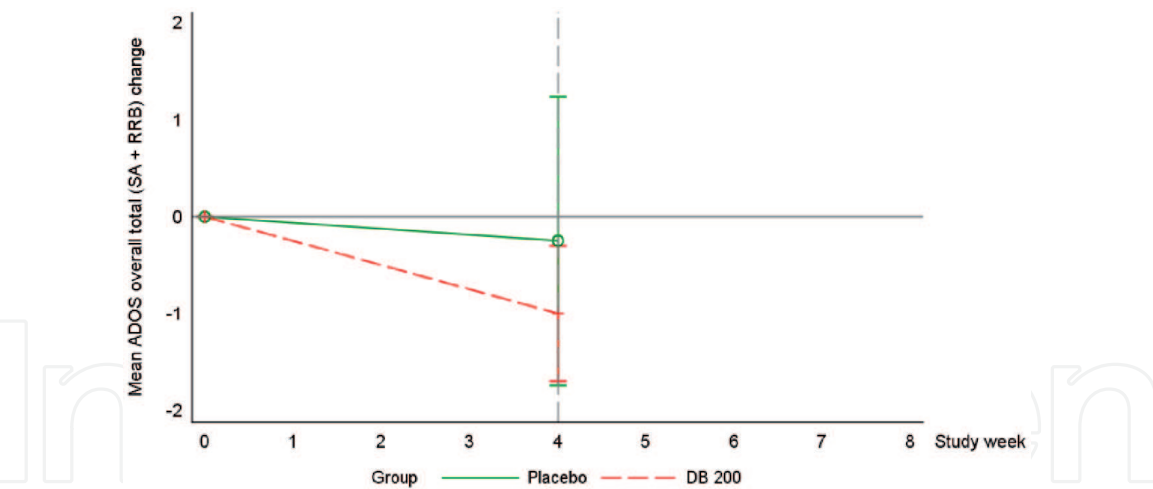
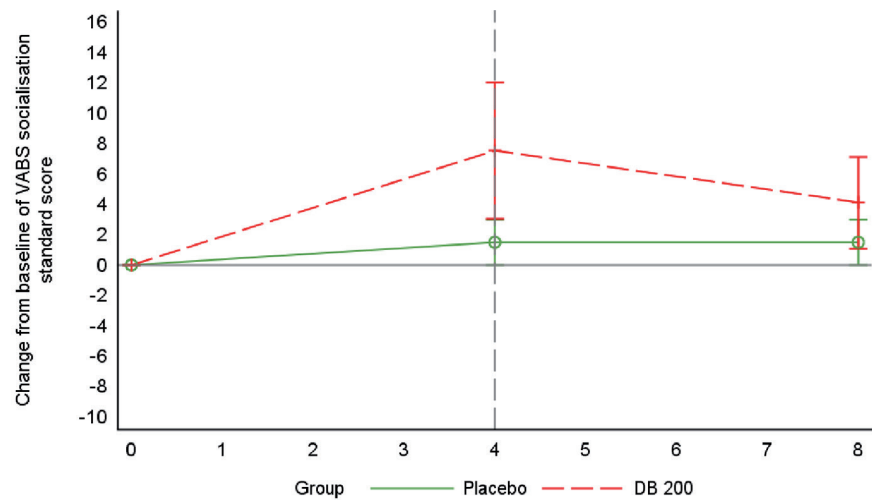


Figure 7.
Pilot study: ADOS score changes for 200 mg dose and placebo after 28 days of treatment. Negative scores represent improvement.



Vertical reference line at Week 4 indicates end of treatment
Intervals are ± 1 standard error
The last observation carried forward (LOCF) approach is applied for subjects with missing data at Week 3 and Week 4.

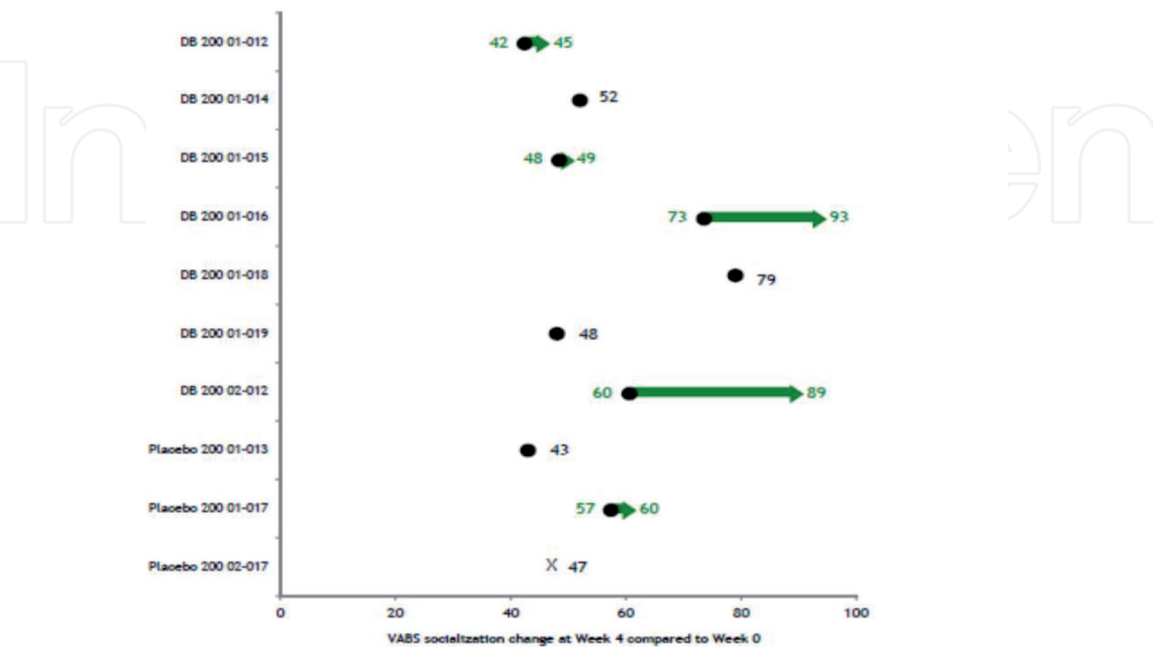


Figure 8.
Upper panel: Change from baseline over time and individual patient responses Vineland adaptive behavior-II (VABS) socialization standard score at week 4 for L1-79 200 mg and placebo. Lower panel individual changes for L1-79 200 mg and placebo.

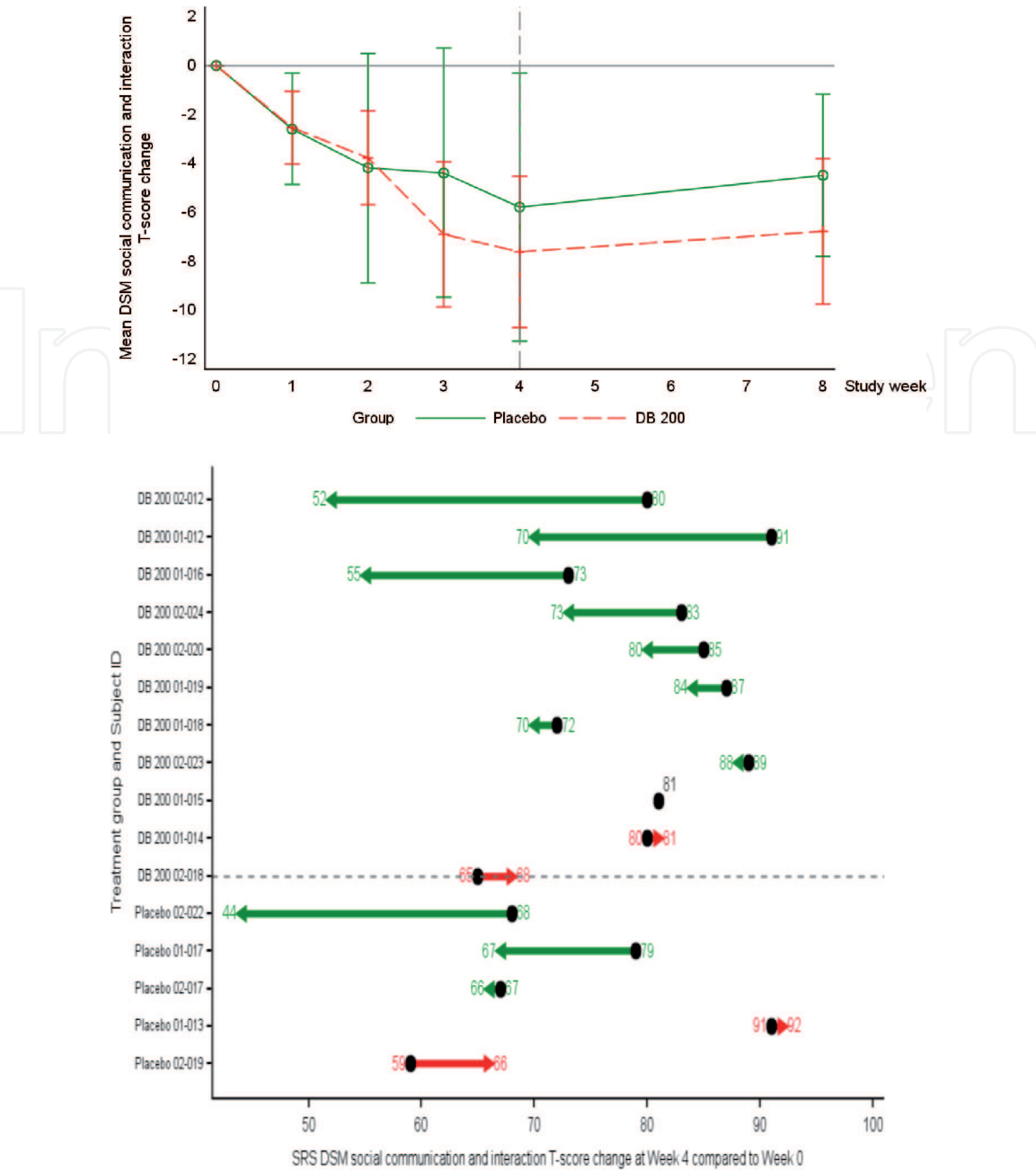


Figure 9. Pilot study: Upper panel is the change from baseline over time in the social responses scale – 2 DSM-SCI for week 4 L1-79 200 mg and placebo. Lower panel individual changes for L1-79 200 mg and placebo.

10. Mechanism of action

We hypothesize that the mechanism begins with some process that stimulates massive levels of sympathetic neural traffic that gives rise to high levels of catecholamine synthesis and release which is associated with high levels of both BDNF and NGF [238]. NGF receptors are found on sympathetic nerves [239] and are responsible for maintaining catecholaminergic synaptic architecture due to their control on the budding and arborization of catecholamine dendrites [207, 208] and density of innervation [209, 210].

Elevated levels of synaptic nerve growth factors associated with catecholamine release may result from a variety of factors including genetics, cognitive or biological stress such as exposure to pesticides, fever in utero, complications of pregnancy, or other causes. This catecholamine elevation results in elevated levels of nerve traffic due to growth factor induced budding and arborization of catecholamine

nerve terminals and collaterals. As these growth factors are required to support the dendritic architecture of the neurons over their life, this elevated level of NGF & BDNF become chronic, resulting in an enhanced level of synaptic morphology and a consequent elevation of catecholamine release from these new hypertrophic synapses. This change in the level of catecholaminergic tone and the elevated release of catecholamines creates a persistent imbalance in the CNS and between the sympathetic and parasympathetic arms of the autonomic nervous system resulting in an overstimulation of some tracts and depletion in others. This imbalance caused by the growth factors centrally and peripherally results in both neurologic and metabolic pathology.

Because this involves catecholaminergic mechanisms in the brain, gut, mesentery, and elsewhere in the body, changes in emotional expression, speech, cognition, memory, circadian rhythms, gut function, energy metabolism, and the entire panoply of autism related symptoms can potentially be ascribed to aberrant catecholaminergic function. It is worth noting that NGF exerts presynaptic functionality with both pre- and post-synaptic effects with both short- and long-term effects on catecholaminergic neurotransmission [216]. Thus, the effects of L1-79 are not mimicked by receptor blocking agents which only reduce post-synaptic depolarization but do nothing to address the underlying abnormality of excessive catecholaminergic collaterals and a hypertrophic dendritic architecture induced and maintained by growth factors.

Since NGF is known to stimulate TH [215, 240–242] and L1-79 inhibits TH, and given both the short and long term effects of NGF exposure on sympathetic substrates, L1-79 is likely to have a therapeutic effect in the short and intermediate term of treatment of autism and may even have a disease modifying effect in the long run if the hypertrophic synaptic architecture regresses to a more homeostatic morphology. That is, if the underlying pathology of ASD is due in whole or part due to elevated catecholaminergic tone due to the release of growth factors associated with catecholamine release, then by reducing catecholamine synthesis, storage and release along with the associated release of NGF and BDNF a reduction of symptoms is likely to result. If, over a longer period, the reduction of NGF and BDNF enables a restoration of normal synaptic morphology then a persistent reduction of ASD symptoms may be possible, even in the absence of treatment.

11. Conclusions

L1-79 inhibits the rate limiting step in the synthesis of catecholamine, including dopamine and norepinephrine. Unlike the L-isomer of AMPT (Demser), L1-79 has a better kinetic profile for the use of L1-79 as a treatment for ASD. Its presynaptic mechanism of action likely results in a diminution of both catecholamines and related growth factors which we hypothesize will reduce symptoms of ASD in a manner not possible with receptor blockers, and which with long term use may reduce the hypertrophic architecture of catecholamine synapses in ASD back to a homeostatic morphology. An exaggerated catecholaminergic mechanism underlying ASD and its associated comorbidities can explain a variety of potential influences on the disease including the effects of bile, orphan receptors, lipids, glucose and other factors.

Preliminary results observed following the administration of L1-79 to autistic juveniles and adolescents has resulted in consistent improvement in the core symptoms of in two early studies [214, 215] not seen with previous agents.

L1-79 appears to be an effective therapy for the treatment of autism in children empirically with a novel mechanism of action that is supported by the scientific literature.

Acknowledgements

The author wishes to acknowledge the inventorship and collegiality of Steve Hoffman.

Conflict of interest

Dr. Rothman is the managing director of Yamo Pharmaceuticals.

Author details

John Rothman^{1,2}

1 Yamo Pharmaceuticals, New York, NY, USA

2 77 Bissell Rd., Lebanon, NJ 08833, USA

*Address all correspondence to: jrothman@yamopharma.com

IntechOpen

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] *Autism Spectrum disorder*. 2015; Available from: <http://www.eu-aims.eu/en/autism-spectrum-disorder-asd/>.
- [2] Geschwind, D.H., *Advances in autism*. Annu Rev Med, 2009. **60**: p. 367-80.
- [3] Goldstein, S. and A.J. Schwebach, *The comorbidity of Pervasive Developmental Disorder and Attention Deficit Hyperactivity Disorder: results of a retrospective chart review*. J Autism Dev Disord, 2004. **34**(3): p. 329-39.
- [4] Simonoff, E., et al., *Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample*. J Am Acad Child Adolesc Psychiatry, 2008. **47**(8): p. 921-9.
- [5] Control, C.f.D. *Data & Statistics on Autism Spectrum Disorder*. 2019; Available from: <https://www.cdc.gov/ncbddd/autism/data.html>.
- [6] Autismnj.org, *1 in 68 in US 1 in 46 in NJ*. 2015.
- [7] O'Brien, K., *Autism Continues to Climb*. Star Ledger, 2014.
- [8] *Autism on the Rise*. 2015; Available from: <http://www.courierpostonline.com/story/opinion/2014/04/20/forum-autism-rise/7916351>.
- [9] Weiss, J.A., et al., *Health Concerns and Health Service Utilization in a Population Cohort of Young Adults with Autism Spectrum Disorder*. J Autism Dev Disord.
- [10] Kershaw, A. "Worrying Rise" in number of children with autism being expelled or suspended from school. The Independent 2017; Available from: <http://www.independent.co.uk/news/education/education-news/autism-expulsion-rate-rise-school-pupils-students-department-education-asd-a7946701.html>.
- [11] Hirvikoski, T., et al., *Premature mortality in autism spectrum disorder*. Br J Psychiatry, 2016. **208**(3): p. 232-8.
- [12] Mayes SD, C.S., Baweja R, Mahr F., *Suicide ideation and attempts in children with psychiatric disorders and typical development*. Crisis, 2015. **36**(1): p. 55-60.
- [13] Paquette-Smith, M., J. Weiss, and Y. Lunskey, *History of suicide attempts in adults with Asperger syndrome*. Crisis, 2014. **35**(4): p. 273-7.
- [14] Takara, K. and T. Kondo, *Comorbid atypical autistic traits as a potential risk factor for suicide attempts among adult depressed patients: a case-control study*. Ann Gen Psychiatry, 2014. **13**(1): p. 33.
- [15] Bennett, M., *The importance of interviewing adults on the autism spectrum about their depression and suicidal ideation experiences*. J. Autism Dev Discord, 2015. **2016**(46): p. 1492-93.
- [16] Cassidy, S., et al., *Suicidal ideation and suicide plans or attempts in adults with Asperger's syndrome attending a specialist diagnostic clinic: a clinical cohort study*. Lancet Psychiatry. **1**(2): p. 142-7.
- [17] Thienpont, L., et al., *Euthanasia requests, procedures and outcomes for 100 Belgian patients suffering from psychiatric disorders: a retrospective, descriptive study*. BMJ Open, 2014. **5**(7): p. e007454.
- [18] Huquet G, C.Y., Doyen C., *Autism spectrum disorder and suicidality*. Encephale, 2015. **41**(4): p. 362-9.
- [19] Kushki, A., et al., *Functional autonomic nervous system profile in children with autism spectrum disorder*. Mol Autism, 2014. **5**: p. 39.
- [20] Fatemi, S.H., et al., *Consensus paper: pathological role of the cerebellum*

in autism. *Cerebellum*, 2012. **11**(3): p. 777-807.

[21] Valenti, D., de Bari, L, De Fillippis, B, Henrion-Caupe, A., Vacca, Ra, *Mitochondrial dysfunction as a central actor in intellectual disability-related diseases: an overview of Down syndrome, autism, Fragile X and Rettsyndrome*. 2014. *Neurosci Biobehav. Rev.*: p. 2.

[22] Rossignol, D.A., Frye, R.E., *A review of research trends in physiological abnormalities in autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and environmental toxicant exposures*. *Mol. Psych.*, 2012. **17**(4): p. 389-401.

[23] Ebisch, S.J., et al., *Altered intrinsic functional connectivity of anterior and posterior insula regions in high-functioning participants with autism spectrum disorder*. *Hum Brain Mapp*, 2011. **32**(7): p. 1013-28.

[24] Uddin, L.Q. and V. Menon, *The anterior insula in autism: under-connected and under-examined*. *Neurosci Biobehav Rev*, 2009. **33**(8): p. 1198-203.

[25] Nordahl, C.W., et al., *Increased rate of amygdala growth in children aged 2 to 4 years with autism spectrum disorders: a longitudinal study*. *Arch Gen Psychiatry*, 2012. **69**(1): p. 53-61.

[26] Schumann, C.M., et al., *Amygdala enlargement in toddlers with autism related to severity of social and communication impairments*. *Biol Psychiatry*, 2009. **66**(10): p. 942-9.

[27] Schumann, C.M., et al., *The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages*. *J Neurosci*, 2004. **24**(28): p. 6392-401.

[28] Bai E., H., E., Lamb D, Van Hecke AV, Denver JW Poges SW,

Emotion recongition in children with autism spectrum disorders Relations to eye gaze and autonomic state. *J. Autism Dev Discord*, 2010. **40**(3): p. 458-70.

[29] Ming, X., et al., *Reduced cardiac parasympathetic activity in children with autism*. *Brain Dev*, 2005. **27**(7): p. 509-16.

[30] Neuhaus, E., R. Bernier, and T.P. Beauchaine, *Brief report: social skills, internalizing and externalizing symptoms, and respiratory sinus arrhythmia in autism*. *J Autism Dev Disord*, 2014. **44**(3): p. 730-7.

[31] Porges, S.W., et al., *Respiratory sinus arrhythmia and auditory processing in autism: modifiable deficits of an integrated social engagement system?* *Int J Psychophysiol*, 2013. **88**(3): p. 261-70.

[32] Jansen, L.M., et al., *Autonomic and neuroendocrine responses to a psychosocial stressor in adults with autistic spectrum disorder*. *J Autism Dev Disord*, 2006. **36**(7): p. 891-9.

[33] Smeekens, I., R. Didden, and E.W. Verhoeven, *Exploring the relationship of autonomic and endocrine activity with social functioning in adults with autism spectrum disorders*. *J Autism Dev Disord*, 2013. **45**(2): p. 495-505.

[34] Patriquin, M.A., J. Lorenzi, and A. Scarpa, *Relationship between respiratory sinus arrhythmia, heart period, and caregiver-reported language and cognitive delays in children with autism spectrum disorders*. *Appl Psychophysiol Biofeedback*, 2013. **38**(3): p. 203-7.

[35] Patriquin, M.A., et al., *Respiratory sinus arrhythmia: a marker for positive social functioning and receptive language skills in children with autism spectrum disorders*. *Dev Psychobiol*, 2013. **55**(2): p. 101-12.

[36] Friedman, B.H. and J.F. Thayer, *Autonomic balance revisited: panic*

anxiety and heart rate variability. J Psychosom Res, 1998. **44**(1): p. 133-51.

[37] Kawachi, I., et al., *Decreased heart rate variability in men with phobic anxiety (data from the Normative Aging Study).* Am J Cardiol, 1995. **75**(14): p. 882-5.

[38] Thayer, J.F., B.H. Friedman, and T.D. Borkovec, *Autonomic characteristics of generalized anxiety disorder and worry.* Biol Psychiatry, 1996. **39**(4): p. 255-66.

[39] Cath, D.C., et al., *Symptom overlap between autism spectrum disorder, generalized social anxiety disorder and obsessive-compulsive disorder in adults: a preliminary case-controlled study.* Psychopathology, 2008. **41**(2): p. 101-10.

[40] van Steensel, F.J., S.M. Bogels, and S. Perrin, *Anxiety disorders in children and adolescents with autistic spectrum disorders: a meta-analysis.* Clin Child Fam Psychol Rev, 2011. **14**(3): p. 302-17.

[41] Mathew, S.J., R.B. Price, and D.S. Charney, *Recent advances in the neurobiology of anxiety disorders: implications for novel therapeutics.* Am J Med Genet C Semin Med Genet, 2008. **148C**(2): p. 89-98.

[42] Shin, L.M. and I. Liberzon, *The neurocircuitry of fear, stress, and anxiety disorders.* Neuropsychopharmacology. **35**(1): p. 169-91.

[43] Kaland, N., et al., *Performance of children and adolescents with Asperger syndrome or high-functioning autism on advanced theory of mind tasks.* J Autism Dev Disord, 2008. **38**(6): p. 1112-23.

[44] Tyson, K.E. and D.G. Cruess, *Differentiating high-functioning autism and social phobia.* J Autism Dev Disord, 2012. **42**(7): p. 1477-90.

[45] van Steensel, F.J., S.M. Bogels, and J.J. Wood, *Autism spectrum traits in*

children with anxiety disorders. J Autism Dev Disord, 2013. **43**(2): p. 361-70.

[46] Hamilton, P., Campbell, NG, Sharma S, Erreger, K, Hansen FH, Saunders, C Belovich, AN, Sahai, MA, Cook, EH, Gether, U, Mchaourab HS, Mathies, HJG, Sutcliffe, JS Galli, A, *De novo mutation in the dopamine transporter gene associates dopamine dysfunction with autism spectrum disorder.* Mol Psychiatry., 2013. **18**(12): p. 1315-23.

[47] Bjorklund, A. and S.B. Dunnett, *Fifty years of dopamine research.* Trends Neurosci, 2007. **30**(5): p. 185-7.

[48] Carlsson, A., *Perspectives on the discovery of central monoaminergic neurotransmission.* Annu Rev Neurosci, 1987. **10**: p. 19-40.

[49] Giros, B. and M.G. Caron, *Molecular characterization of the dopamine transporter.* Trends Pharmacol Sci, 1993. **14**(2): p. 43-9.

[50] Palmiter, R.D., *Dopamine signaling in the dorsal striatum is essential for motivated behaviors: lessons from dopamine-deficient mice.* Ann N Y Acad Sci, 2008. **1129**: p. 35-46.

[51] Gadow, K.D., C.J. DeVincent, and J. Pomeroy, *ADHD symptom subtypes in children with pervasive developmental disorder.* J Autism Dev Disord, 2006. **36**(2): p. 271-83.

[52] Sturm, H., E. Fernell, and C. Gillberg, *Autism spectrum disorders in children with normal intellectual levels: associated impairments and subgroups.* Dev Med Child Neurol, 2004. **46**(7): p. 444-7.

[53] Yoshida, Y. and T. Uchiyama, *The clinical necessity for assessing Attention Deficit/Hyperactivity Disorder (AD/HD) symptoms in children with high-functioning Pervasive Developmental Disorder (PDD).* Eur Child Adolesc Psychiatry, 2004. **13**(5): p. 307-14.

- [54] Hettinger, J.A., et al., *A DRD1 haplotype is associated with risk for autism spectrum disorders in male-only affected sib-pair families*. Am J Med Genet B Neuropsychiatr Genet, 2008. **147B**(5): p. 628-36.
- [55] de Krom, M., et al., *A common variant in DRD3 receptor is associated with autism spectrum disorder*. Biol Psychiatry, 2009. **65**(7): p. 625-30.
- [56] Gadow, K.D., et al., *Association of DRD4 polymorphism with severity of oppositional defiant disorder, separation anxiety disorder and repetitive behaviors in children with autism spectrum disorder*. Eur J Neurosci, 2010. **32**(6): p. 1058-65.
- [57] Staal, W.G., M. de Krom, and M.V. de Jonge, *Brief report: the dopamine-3-receptor gene (DRD3) is associated with specific repetitive behavior in autism spectrum disorder (ASD)*. J Autism Dev Disord, 2012. **42**(5): p. 885-8.
- [58] Tassone, F., et al., *MAOA, DBH, and SLC6A4 variants in CHARGE: a case-control study of autism spectrum disorders*. Autism Res, 2011. **4**(4): p. 250-61.
- [59] Hettinger, J.A., et al., *DRD2 and PPP1R1B (DARPP-32) polymorphisms independently confer increased risk for autism spectrum disorders and additively predict affected status in male-only affected sib-pair families*. Behav Brain Funct, 2012. **8**: p. 19.
- [60] Qian, Y., et al., *Genetic variation in dopamine-related gene expression influences motor skill learning in mice*. Genes Brain Behav, 2013. **12**(6): p. 604-14.
- [61] Reiersen, A.M. and A.A. Todorov, *Association between DRD4 genotype and Autistic Symptoms in DSM-IV ADHD*. J Can Acad Child Adolesc Psychiatry, 2011. **20**(1): p. 15-21.
- [62] Diler SR, F.S., Avci A., *An open-label trial of risperidone in with autism*. Current Therapeutic Research, 2002. **63**(1): p. 91-102.
- [63] Hosenbocus, S. and R. Chahal, *A review of executive function deficits and pharmacological management in children and adolescents*. J Can Acad Child Adolesc Psychiatry, 2012. **21**(3): p. 223-9.
- [64] Garnier, C., et al., *Dopamine-beta-hydroxylase (DBH) and homovanillic acid (HVA) in autistic children*. J Autism Dev Disord, 1986. **16**(1): p. 23-9.
- [65] Lake, C.R., M.G. Ziegler, and D.L. Murphy, *Increased norepinephrine levels and decreased dopamine-beta-hydroxylase activity in primary autism*. Arch Gen Psychiatry, 1977. **34**(5): p. 553-6.
- [66] Launay, J.M., et al., *Catecholamines metabolism in infantile autism: a controlled study of 22 autistic children*. J Autism Dev Disord, 1987. **17**(3): p. 333-47.
- [67] Martineau, J., et al., *Monoamines (serotonin and catecholamines) and their derivatives in infantile autism: age-related changes and drug effects*. Dev Med Child Neurol, 1992. **34**(7): p. 593-603.
- [68] Damasio, A.R. and R.G. Maurer, *A neurological model for childhood autism*. Arch Neurol, 1978. **35**(12): p. 777-86.
- [69] Maurer, R.G. and A.R. Damasio, *Childhood autism from the point of view of behavioral neurology*. J Autism Dev Disord, 1982. **12**(2): p. 195-205.
- [70] Nguyen, M., et al., *Decoding the contribution of dopaminergic genes and pathways to autism spectrum disorder (ASD)*. Neurochem Int, 2014. **66**: p. 15-26.
- [71] Yagishita, S., et al., *A critical time window for dopamine actions on the structural plasticity of dendritic spines*. Science, 2014. **345**(6204): p. 1616-20.

- [72] Kriete, T. and D.C. Noelle, *Dopamine and the development of executive dysfunction in autism spectrum disorders*. PLoS One. **10**(3): p. e0121605.
- [73] Courchesne, E., *Brainstem, cerebellar and limbic neuroanatomical abnormalities in autism*. Curr Opin Neurobiol, 1997. **7**(2): p. 269-78.
- [74] Courchesne, E., et al., *Impairment in shifting attention in autistic and cerebellar patients*. Behav Neurosci, 1994. **108**(5): p. 848-65.
- [75] Courchesne, E., et al., *Hypoplasia of cerebellar vermal lobules VI and VII in autism*. N Engl J Med, 1988. **318**(21): p. 1349-54.
- [76] Palmen, S.J., et al., *Neuropathological findings in autism*. Brain, 2004. **127**(Pt 12): p. 2572-83.
- [77] Webb, S.J., et al., *Cerebellar vermal volumes and behavioral correlates in children with autism spectrum disorder*. Psychiatry Res, 2009. **172**(1): p. 61-7.
- [78] Martin, L.A., D. Goldowitz, and G. Mittleman, *Repetitive behavior and increased activity in mice with Purkinje cell loss: a model for understanding the role of cerebellar pathology in autism*. Eur J Neurosci, 2010. **31**(3): p. 544-55.
- [79] Rogers, T.D., et al., *Reorganization of circuits underlying cerebellar modulation of prefrontal cortical dopamine in mouse models of autism spectrum disorder*. Cerebellum, 2013. **12**(4): p. 547-56.
- [80] Kirsten, T.B., et al., *Hypoactivity of the central dopaminergic system and autistic-like behavior induced by a single early prenatal exposure to lipopolysaccharide*. J Neurosci Res, 2012. **90**(10): p. 1903-12.
- [81] Meyer, U., et al., *Preliminary evidence for a modulation of fetal dopaminergic development by maternal immune activation during pregnancy*. Neuroscience, 2008. **154**(2): p. 701-9.
- [82] Liaw, D., et al., *Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome*. Nat Genet, 1997. **16**(1): p. 64-7.
- [83] Tilot, A.K., et al., *Germline disruption of Pten localization causes enhanced sex-dependent social motivation and increased glial production*. Hum Mol Genet, 2014. **23**(12): p. 3212-27.
- [84] Zhang, Y., et al., *PTEN deletion enhances survival, neurite outgrowth and function of dopamine neuron grafts to MitoPark mice*. Brain, 2012. **135**(Pt 9): p. 2736-49.
- [85] He, X., et al., *Cytoplasm-predominant Pten associates with increased region-specific brain tyrosine hydroxylase and dopamine D2 receptors in mouse model with autistic traits*. Mol Autism, 2015. **6**: p. 63.
- [86] D'Souza, A., et al., *Valproic acid regulates catecholaminergic pathways by concentration-dependent threshold effects on TH mRNA synthesis and degradation*. Brain Res, 2009. **1247**: p. 1-10.
- [87] Black, C., J.A. Kaye, and H. Jick, *Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database*. Bmj, 2002. **325**(7361): p. 419-21.
- [88] Horvath, K., et al., *Gastrointestinal abnormalities in children with autistic disorder*. J Pediatr, 1999. **135**(5): p. 559-63.
- [89] Sabra, A., J.A. Bellanti, and A.R. Colon, *Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children*. Lancet, 1998. **352**(9123): p. 234-5.

- [90] He, X., et al., *Cytoplasm-predominant Pten associates with increased region-specific brain tyrosine hydroxylase and dopamine D2 receptors in mouse model with autistic traits*. Mol Autism, 2015. **6**: p. 63.
- [91] D'Souza, A., et al., *Valproic acid regulates catecholaminergic pathways by concentration-dependent threshold effects on TH mRNA synthesis and degradation*. Brain Res, 2009. **1247**: p. 1-10.
- [92] Wang, L.W., D.J. Tancredi, and D.W. Thomas, *The prevalence of gastrointestinal problems in children across the United States with autism spectrum disorders from families with multiple affected members*. J Dev Behav Pediatr, 2011. **32**(5): p. 351-60.
- [93] Ellingson, B.M., et al., *Diffusion tensor imaging detects microstructural reorganization in the brain associated with chronic irritable bowel syndrome*. Pain, 2013. **154**(9): p. 1528-41.
- [94] Green, S.A., et al., *Overreactive brain responses to sensory stimuli in youth with autism spectrum disorders*. J Am Acad Child Adolesc Psychiatry, 2013. **52**(11): p. 1158-72.
- [95] Mayer, E.A., D. Padua, and K. Tillisch, *Altered brain-gut axis in autism: comorbidity or causative mechanisms?* Bioessays, 2014. **36**(10): p. 933-9.
- [96] Mayer, E.A., T. Savidge, and R.J. Shulman, *Brain-gut microbiome interactions and functional bowel disorders*. Gastroenterology, 2014. **146**(6): p. 1500-12.
- [97] Cryan JF, M.S., *The microbiome-gut-brain axis: from bowel to behavior*. Neurogastroenterology and Motility, 2011. **23**: p. 187-92.
- [98] Sandrini S, A.M., Alruways M, Freestone P, *Microbial endocrinology: host-bacteria communicatino with the gut microbiome*. Journal of Endocrinology, 2015. **225**: p. R21-34.
- [99] Lightdale JR, S.B., Heyman MB, *Gastrointestinal symptoms in autistic children*. Clin. Perspect Gastroenterol, 2001. **1**: p. 56-58.
- [100] White, J.F., *Intestinal pathophysiology in autism*. Exp Biol Med (Maywood), 2003. **228**(6): p. 639-49.
- [101] Lucarelli, S., et al., *Food allergy and infantile autism*. Panminerva Med, 1995. **37**(3): p. 137-41.
- [102] Israngkun, P.P., et al., *Potential biochemical markers for infantile autism*. Neurochem Pathol, 1986. **5**(1): p. 51-70.
- [103] Knivsberg A, R.K., Nodland N, Hoen T, *Autistic syndromes and diet: a follow-up study*. Scand J Educ Res, 1995. **39**: p. 223-36.
- [104] Reichelt KL, K.A., Lind G, Nodland M., *Probable etiology and possible treatment of childhood autism*. Brain Dysfunct, 1991. **4**: p. 308-319.
- [105] Shattock P, K.A., Rowell F, Berney TP., *Role of neuropeptides in autism and their relationships with classical neurotransmitters*. Brain Dysfunct, 1990. **3**: p. 328-45.
- [106] D'Eufemia, P., et al., *Abnormal intestinal permeability in children with autism*. Acta Paediatr, 1996. **85**(9): p. 1076-9.
- [107] Reichelt KL, E.J., Scott H., *Gluten, milk proteins and autism: dietary intervention effects on behavior and peptide secretion*. J Appl Nutr, 1990. **42**: p. 1-11.
- [108] Lindstrom, L.H., et al., *CSF and plasma beta-casomorphin-like opioid peptides in postpartum psychosis*. Am J Psychiatry, 1984. **141**(9): p. 1059-66.
- [109] Sun Z, C.J., Fregly MJ, Privette RM., *-Casomorphin induces*

Fos-like immunoreactivity in discrete brain regions relevant to schizophrenia and autism. Autism Res, 1999. 3: p. 67-83.

[110] Macfabe, D.F., *Short-chain fatty acid fermentation products of the gut microbiome: implications in autism spectrum disorders.* Microb Ecol Health Dis. 23.

[111] Frye, R.E., S. Melnyk, and D.F. Macfabe, *Unique acyl-carnitine profiles are potential biomarkers for acquired mitochondrial disease in autism spectrum disorder.* Transl Psychiatry, 2013. 3: p. e220.

[112] Al-Lahham, S.H., et al., *Biological effects of propionic acid in humans; metabolism, potential applications and underlying mechanisms.* Biochim Biophys Acta, 2010. 1801(11): p. 1175-83.

[113] Aranyi, T., et al., *Sodium butyrate modifies the stabilizing complexes of tyrosine hydroxylase mRNA.* Biochem Biophys Res Commun, 2007. 359(1): p. 15-9.

[114] Ebert, S.N., et al., *Adrenergic differentiation potential in PC12 cells: influence of sodium butyrate and dexamethasone.* Brain Res Mol Brain Res, 1997. 47(1-2): p. 24-30.

[115] Nankova, B.B., et al., *Nicotinic induction of preproenkephalin and tyrosine hydroxylase gene expression in butyrate-differentiated rat PC12 cells: a model for adaptation to gut-derived environmental signals.* Pediatr Res, 2003. 53(1): p. 113-8.

[116] Parab, S., B.B. Nankova, and E.F. La Gamma, *Differential regulation of the tyrosine hydroxylase and enkephalin neuropeptide transmitter genes in rat PC12 cells by short chain fatty acids: concentration-dependent effects on transcription and RNA stability.* Brain Res, 2007. 1132(1): p. 42-50.

[117] Nankova, B.B., et al., *Enteric bacterial metabolites propionic*

and butyric acid modulate gene expression, including CREB-dependent catecholaminergic neurotransmission, in PC12 cells--possible relevance to autism spectrum disorders. PLoS One. 9(8): p. e103740.

[118] McCracken, J.T., et al., *Risperidone in children with autism and serious behavioral problems.* N Engl J Med, 2002. 347(5): p. 314-21.

[119] McDougle, C.J., et al., *Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology.* Am J Psychiatry, 2005. 162(6): p. 1142-8.

[120] Christensen, J., et al., *Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism.* Jama, 2013. 309(16): p. 1696-703.

[121] Cohen, O.S., et al., *Acute prenatal exposure to a moderate dose of valproic acid increases social behavior and alters gene expression in rats.* Int J Dev Neurosci, 2013. 31(8): p. 740-50.

[122] Ingram, J.L., et al., *Prenatal exposure of rats to valproic acid reproduces the cerebellar anomalies associated with autism.* Neurotoxicol Teratol, 2000. 22(3): p. 319-24.

[123] Asano, Y., et al., *Critical role of gut microbiota in the production of biologically active, free catecholamines in the gut lumen of mice.* Am J Physiol Gastrointest Liver Physiol, 2012. 303(11): p. G1288-95.

[124] Lyte, M., *The biogenic amine tyramine modulates the adherence of Escherichia coli O157:H7 to intestinal mucosa.* J Food Prot, 2004. 67(5): p. 878-83.

[125] Lyte, M., *Microbial endocrinology and infectious disease in the 21st century.* Trends Microbiol, 2004. 12(1): p. 14-20.

- [126] Lyte, M. and S. Ernst, *Alpha and beta adrenergic receptor involvement in catecholamine-induced growth of gram-negative bacteria*. Biochem Biophys Res Commun, 1993. **190**(2): p. 447-52.
- [127] Bansal, T., et al., *Differential effects of epinephrine, norepinephrine, and indole on Escherichia coli O157:H7 chemotaxis, colonization, and gene expression*. Infect Immun, 2007. **75**(9): p. 4597-607.
- [128] Mally, P., et al., *Stereospecific regulation of tyrosine hydroxylase and proenkephalin genes by short-chain fatty acids in rat PC12 cells*. Pediatr Res, 2004. **55**(5): p. 847-54.
- [129] Le Menn, G. and J.G. Neels, *Regulation of Immune Cell Function by PPARs and the Connection with Metabolic and Neurodegenerative Diseases*. Int J Mol Sci, 2018. **19**(6).
- [130] Flemstrom, G., B. Safsten, and G. Jedstedt, *Stimulation of mucosal alkaline secretion in rat duodenum by dopamine and dopaminergic compounds*. Gastroenterology, 1993. **104**(3): p. 825-33.
- [131] Iwatsuki, K., L.M. Ren, and S. Chiba, *Effects of YM435, a novel dopamine D1 receptor agonist, on pancreatic exocrine secretion in anesthetized dogs*. Eur J Pharmacol, 1992. **218**(2-3): p. 237-41.
- [132] Finkel, Y., et al., *Endogenous dopamine modulates jejunal sodium absorption during high-salt diet in young but not in adult rats*. Gastroenterology, 1994. **107**(3): p. 675-9.
- [133] Glavin, G.B. and A.M. Hall, *Central and peripheral dopamine D1/DA1 receptor modulation of gastric secretion and experimental gastric mucosal injury*. Gen Pharmacol, 1995. **26**(6): p. 1277-9.
- [134] Glavin, G.B. and S. Szabo, *Dopamine in gastrointestinal disease*. Dig Dis Sci, 1990. **35**(9): p. 1153-61.
- [135] Haskel, Y. and M. Hanani, *Inhibition of gastrointestinal motility by MPTP via adrenergic and dopaminergic mechanisms*. Dig Dis Sci, 1994. **39**(11): p. 2364-7.
- [136] Martineau, J., et al., *Catecholaminergic metabolism and autism*. Dev Med Child Neurol, 1994. **36**(8): p. 688-97.
- [137] Bachevalier, J. and K.A. Loveland, *The orbitofrontal-amygdala circuit and self-regulation of social-emotional behavior in autism*. Neurosci Biobehav Rev, 2006. **30**(1): p. 97-117.
- [138] Baron-Cohen, S., et al., *The amygdala theory of autism*. Neurosci Biobehav Rev, 2000. **24**(3): p. 355-64.
- [139] Eisenhofer, G., et al., *Substantial production of dopamine in the human gastrointestinal tract*. J Clin Endocrinol Metab, 1997. **82**(11): p. 3864-71.
- [140] Eisenhofer, G., et al., *Production and metabolism of dopamine and norepinephrine in mesenteric organs and liver of swine*. Am J Physiol, 1995. **268**(4 Pt 1): p. G641-9.
- [141] Koetting, M., J. Stegemann, and T. Minor, *Dopamine as additive to cold preservation solution improves postischemic integrity of the liver*. Transpl Int, 2010. **23**(9): p. 951-8.
- [142] Minor, T., B. Luer, and P. Efferz, *Dopamine improves hypothermic machine preservation of the liver*. Cryobiology, 2011. **63**(2): p. 84-9.
- [143] McMillin, M., et al., *Bile Acid Signaling Is Involved in the Neurological Decline in a Murine Model of Acute Liver Failure*. Am J Pathol, 2016.
- [144] Quinn, M., et al., *Bile acids permeabilize the blood brain barrier after bile duct ligation in rats via Rac1-dependent mechanisms*. Dig Liver Dis. **46**(6): p. 527-34.

- [145] Mano, N., et al., *Presence of protein-bound unconjugated bile acids in the cytoplasmic fraction of rat brain*. J Lipid Res, 2004. **45**(2): p. 295-300.
- [146] Quinn, M., et al., *Bile acids permeabilize the blood brain barrier after bile duct ligation in rats via Rac1-dependent mechanisms*. Dig Liver Dis, 2014. **46**(6): p. 527-34.
- [147] Fombonne, E., *Epidemiological surveys of autism and other pervasive developmental disorders: an update*. J Autism Dev Disord, 2003. **33**(4): p. 365-82.
- [148] Gillberg, C., et al., *Brief report: "the autism epidemic". The registered prevalence of autism in a Swedish urban area*. J Autism Dev Disord, 2006. **36**(3): p. 429-35.
- [149] Loke, H., V. Harley, and J. Lee, *Biological factors underlying sex differences in neurological disorders*. Int J Biochem Cell Biol. **65**: p. 139-50.
- [150] Grissom, N.M., et al., *Male-specific deficits in natural reward learning in a mouse model of neurodevelopmental disorders*. Mol Psychiatry.
- [151] Imbesi, M., et al., *Dopamine receptor-mediated regulation of neuronal "clock" gene expression*. Neuroscience, 2009. **158**(2): p. 537-44.
- [152] Sahar, S., et al., *Regulation of BMAL1 protein stability and circadian function by GSK3beta-mediated phosphorylation*. PLoS One. **5**(1): p. e8561.
- [153] Besharse, J.C., et al., *Regulation of photoreceptor Per1 and Per2 by light, dopamine and a circadian clock*. Eur J Neurosci, 2004. **20**(1): p. 167-74.
- [154] Doi, M., et al., *Impaired light masking in dopamine D2 receptor-null mice*. Nat Neurosci, 2006. **9**(6): p. 732-4.
- [155] Hood, S., et al., *Endogenous dopamine regulates the rhythm of expression of the clock protein PER2 in the rat dorsal striatum via daily activation of D2 dopamine receptors*. J Neurosci. **30**(42): p. 14046-58.
- [156] Schubring, S.R., et al., *The bile steroid chenodeoxycholate is a potent antagonist at NMDA and GABA(A) receptors*. Neurosci Lett, 2012. **506**(2): p. 322-6.
- [157] Yanovsky, Y., et al., *Waking action of ursodeoxycholic acid (UDCA) involves histamine and GABAA receptor block*. PLoS One, 2012. **7**(8): p. e42512.
- [158] Chawla, A., et al., *Nuclear receptors and lipid physiology: opening the X-files*. Science, 2001. **294**(5548): p. 1866-70.
- [159] Claudel, T., B. Staels, and F. Kuipers, *The Farnesoid X receptor: a molecular link between bile acid and lipid and glucose metabolism*. Arterioscler Thromb Vasc Biol, 2005. **25**(10): p. 2020-30.
- [160] Gabbi, C., M. Warner, and J.A. Gustafsson, *Action mechanisms of Liver X Receptors*. Biochem Biophys Res Commun, 2014. **446**(3): p. 647-50.
- [161] Lee, S.D. and P. Tontonoz, *Liver X receptors at the intersection of lipid metabolism and atherogenesis*. Atherosclerosis, 2015. **242**(1): p. 29-36.
- [162] Li, S., et al., *Farnesoid X receptor signal is involved in deoxycholic acid-induced intestinal metaplasia of normal human gastric epithelial cells*. Oncol Rep, 2015. **34**(5): p. 2674-82.
- [163] Ma, K., et al., *Farnesoid X receptor is essential for normal glucose homeostasis*. J Clin Invest, 2006. **116**(4): p. 1102-9.
- [164] Sepe, V., et al., *Farnesoid X receptor modulators (2011-2014): a patent review*. Expert Opin Ther Pat, 2015. **25**(8): p. 885-96.

- [165] Woo, J.H., et al., *Control of Inflammatory Responses: a New Paradigm for the Treatment of Chronic Neuronal Diseases*. Exp Neurobiol, 2015. **24**(2): p. 95-102.
- [166] Cariou, B., et al., *The farnesoid X receptor modulates adiposity and peripheral insulin sensitivity in mice*. J Biol Chem, 2006. **281**(16): p. 11039-49.
- [167] Zhang, Y., et al., *Activation of the nuclear receptor FXR improves hyperglycemia and hyperlipidemia in diabetic mice*. Proc Natl Acad Sci U S A, 2006. **103**(4): p. 1006-11.
- [168] Renga, B., et al., *The bile acid sensor FXR regulates insulin transcription and secretion*. Biochim Biophys Acta, 2010. **1802**(3): p. 363-72.
- [169] Popescu, I.R., et al., *The nuclear receptor FXR is expressed in pancreatic beta-cells and protects human islets from lipotoxicity*. FEBS Lett, 2010. **584**(13): p. 2845-51.
- [170] Waterson, M.J. and T.L. Horvath, *Neuronal Regulation of Energy Homeostasis: Beyond the Hypothalamus and Feeding*. Cell Metab, 2015. **22**(6): p. 962-70.
- [171] Arble, D.M. and D.A. Sandoval, *CNS control of glucose metabolism: response to environmental challenges*. Front Neurosci, 2013. **7**: p. 20.
- [172] Gancheva, S. and M. Roden, *Central Regulation of Glucose Metabolism in Humans: Fact or Fiction?* Diabetes, 2016. **65**(9): p. 2467-9.
- [173] Han, C., M.W. Rice, and D. Cai, *Neuroinflammatory and autonomic mechanisms in diabetes and hypertension*. Am J Physiol Endocrinol Metab, 2016. **311**(1): p. E32-41.
- [174] Morton, G.J. and M.W. Schwartz, *Leptin and the central nervous system control of glucose metabolism*. Physiol Rev, 2011. **91**(2): p. 389-411.
- [175] Havel, P.J., et al., *Role for autonomic nervous system to increase pancreatic glucagon secretion during marked insulin-induced hypoglycemia in dogs*. Diabetes, 1991. **40**(9): p. 1107-14.
- [176] Dietschy, J.M. and S.D. Turley, *Cholesterol metabolism in the brain*. Curr Opin Lipidol, 2001. **12**(2): p. 105-12.
- [177] Hottman, D.A., et al., *HDL and cognition in neurodegenerative disorders*. Neurobiol Dis, 2014. **72 Pt A**: p. 22-36.
- [178] Atzmon, G., et al., *Plasma HDL levels highly correlate with cognitive function in exceptional longevity*. J Gerontol A Biol Sci Med Sci, 2002. **57**(11): p. M712-5.
- [179] Barzilai, N., et al., *A genotype of exceptional longevity is associated with preservation of cognitive function*. Neurology, 2006. **67**(12): p. 2170-5.
- [180] van den Kommer, T.N., et al., *Role of lipoproteins and inflammation in cognitive decline: do they interact?* Neurobiol Aging, 2012. **33**(1): p. 196 e1-12.
- [181] Singh-Manoux, A., et al., *Socioeconomic status moderates the association between carotid intima-media thickness and cognition in midlife: evidence from the Whitehall II study*. Atherosclerosis, 2008. **197**(2): p. 541-8.
- [182] Song, F., et al., *Plasma apolipoprotein levels are associated with cognitive status and decline in a community cohort of older individuals*. PLoS One, 2012. **7**(6): p. e34078.
- [183] van Exel, E., et al., *Association between high-density lipoprotein and cognitive impairment in the oldest old*. Ann Neurol, 2002. **51**(6): p. 716-21.

- [184] Izaks, G.J., et al., *Cholesteryl Ester Transfer Protein (CETP) genotype and cognitive function in persons aged 35 years or older*. *Neurobiol Aging*, 2012. **33**(8): p. 1851 e7-16.
- [185] Sanders, A.E., et al., *Association of a functional polymorphism in the cholesteryl ester transfer protein (CETP) gene with memory decline and incidence of dementia*. *Jama*, 2010. **303**(2): p. 150-8.
- [186] Quinn, M.a.D., S., *Bile in the Brain? A Role for Bile Acids in the Central Nervous System*. *Cell*, 2012. **3**(7).
- [187] Tontonoz, P. and B.M. Spiegelman, *Fat and beyond: the diverse biology of PPARgamma*. *Annu Rev Biochem*, 2008. **77**: p. 289-312.
- [188] Lo, S.H., et al., *Increase of PPARdelta by dopamine mediated via DA-1 receptor-linked phospholipase C pathway in neonatal rat cardiomyocytes*. *Auton Neurosci*, 2013. **177**(2): p. 211-6.
- [189] Arakawa, R., et al., *Fenofibric acid, an active form of fenofibrate, increases apolipoprotein A-I-mediated high-density lipoprotein biogenesis by enhancing transcription of ATP-binding cassette transporter A1 gene in a liver X receptor-dependent manner*. *Arterioscler Thromb Vasc Biol*, 2005. **25**(6): p. 1193-7.
- [190] Nakaya, K., et al., *Peroxisome proliferator-activated receptor-alpha activation promotes macrophage reverse cholesterol transport through a liver X receptor-dependent pathway*. *Arterioscler Thromb Vasc Biol*, 2011. **31**(6): p. 1276-82.
- [191] Ananth, J., et al., *Atypical antipsychotic induced weight gain: pathophysiology and management*. *Ann Clin Psychiatry*, 2004. **16**(2): p. 75-85.
- [192] Kim, E.K., et al., *Alterations in lipid profile of autistic boys: a case control study*. *Nutr Res*, 2010. **30**(4): p. 255-60.
- [193] Vincenzi, B., et al., *An exploratory study examining lipid-lowering medications in reducing fasting serum lipids in schizophrenia patients treated with atypical antipsychotics*. *Ann Clin Psychiatry*, 2013. **25**(2): p. 141-8.
- [194] Grover, S., et al., *Possible beneficial effect of peroxisome proliferator-activated receptor (PPAR)--alpha and gamma agonist against a rat model of oral dyskinesia*. *Pharmacol Biochem Behav*, 2013. **111**: p. 17-23.
- [195] Melis, M., et al., *Peroxisome proliferator-activated receptors-alpha modulate dopamine cell activity through nicotinic receptors*. *Biol Psychiatry*, 2010. **68**(3): p. 256-64.
- [196] Breier, A., et al., *Association of ketamine-induced psychosis with focal activation of the prefrontal cortex in healthy volunteers*. *Am J Psychiatry*, 1997. **154**(6): p. 805-11.
- [197] Jackson, M.E., H. Homayoun, and B. Moghaddam, *NMDA receptor hypofunction produces concomitant firing rate potentiation and burst activity reduction in the prefrontal cortex*. *Proc Natl Acad Sci U S A*, 2004. **101**(22): p. 8467-72.
- [198] Markram, H., et al., *Interneurons of the neocortical inhibitory system*. *Nat Rev Neurosci*, 2004. **5**(10): p. 793-807.
- [199] Wilson, F.A., S.P. O'Scalaidhe, and P.S. Goldman-Rakic, *Functional synergism between putative gamma-aminobutyrate-containing neurons and pyramidal neurons in prefrontal cortex*. *Proc Natl Acad Sci U S A*, 1994. **91**(9): p. 4009-13.
- [200] D'Agostino, G., et al., *Peroxisome proliferator-activated receptor alpha plays a crucial role in behavioral repetition and cognitive flexibility in mice*. *Mol Metab*, 2015. **4**(7): p. 528-36.

- [201] Aloe, L., et al., *Aggressive behavior induces release of nerve growth factor from mouse salivary gland into the bloodstream*. Proc Natl Acad Sci U S A, 1986. **83**(16): p. 6184-7.
- [202] Bantubungi, K., J. Prawitt, and B. Staels, *Control of metabolism by nutrient-regulated nuclear receptors acting in the brain*. J Steroid Biochem Mol Biol. **130**(3-5): p. 126-37.
- [203] Furukawa, S., I. Shinoda, and Y. Furukawa, *[Regulatory mechanisms of nerve growth factor synthesis in vitro]*. Hum Cell, 1989. **2**(2): p. 137-42.
- [204] Harper, G.P. and H. Thoenen, *Nerve growth factor: biological significance, measurement, and distribution*. J Neurochem, 1980. **34**(1): p. 5-16.
- [205] Levi-Montalcini, R., *The nerve growth factor 35 years later*. Science, 1987. **237**(4819): p. 1154-62.
- [206] Levi-Montalcini, R. and P.U. Angeletti, *Nerve growth factor*. Physiol Rev, 1968. **48**(3): p. 534-69.
- [207] Purves, D., W.D. Snider, and J.T. Voyvodic, *Trophic regulation of nerve cell morphology and innervation in the autonomic nervous system*. Nature, 1988. **336**(6195): p. 123-8.
- [208] Snider, W.D., *Nerve growth factor enhances dendritic arborization of sympathetic ganglion cells in developing mammals*. J Neurosci, 1988. **8**(7): p. 2628-34.
- [209] Korsching, S. and H. Thoenen, *Developmental changes of nerve growth factor levels in sympathetic ganglia and their target organs*. Dev Biol, 1988. **126**(1): p. 40-6.
- [210] Shelton, D.L. and L.F. Reichardt, *Expression of the beta-nerve growth factor gene correlates with the density of sympathetic innervation in effector organs*. Proc Natl Acad Sci U S A, 1984. **81**(24): p. 7951-5.
- [211] Paredes, D., A.C. Granholm, and P.C. Bickford, *Effects of NGF and BDNF on baseline glutamate and dopamine release in the hippocampal formation of the adult rat*. Brain Res, 2007. **1141**: p. 56-64.
- [212] Taborsky, G.J., Jr., et al., *The p75 neurotrophin receptor is required for the major loss of sympathetic nerves from islets under autoimmune attack*. Diabetes, 2014. **63**(7): p. 2369-79.
- [213] Eranko O, S.A., Paivarinta, *Histochemistry and cell biology of autonomic neurons in SIF cells and Paraneurons*. 1980, Raven New York.
- [214] Lillien, L.E. and P. Claude, *Nerve growth factor and glucocorticoids regulate phenotypic expression in cultured chromaffin cells from adult rhesus monkeys*. Exp Cell Res, 1985. **161**(2): p. 255-68.
- [215] Otten, U., et al., *Selective induction of tyrosine hydroxylase and dopamine beta-hydroxylase by nerve growth factor: comparison between adrenal medulla and sympathetic ganglia of adult and newborn rats*. Brain Res, 1977. **133**(2): p. 291-303.
- [216] Lockhart, S.T., G.G. Turrigiano, and S.J. Birren, *Nerve growth factor modulates synaptic transmission between sympathetic neurons and cardiac myocytes*. J Neurosci, 1997. **17**(24): p. 9573-82.
- [217] Cowan, W.M., et al., *Regressive events in neurogenesis*. Science, 1984. **225**(4668): p. 1258-65.
- [218] Lipov, E.G., et al., *A unifying theory linking the prolonged efficacy of the stellate ganglion block for the treatment of chronic regional pain syndrome (CRPS), hot flashes, and posttraumatic stress disorder (PTSD)*. Med Hypotheses, 2009. **72**(6): p. 657-61.

- [219] Ting, A.Y., A.D. Blacklock, and P.G. Smith, *Estrogen regulates vaginal sensory and autonomic nerve density in the rat*. Biol Reprod, 2004. **71**(4): p. 1397-404.
- [220] Chen, P.S., et al., *Sympathetic nerve sprouting, electrical remodeling and the mechanisms of sudden cardiac death*. Cardiovasc Res, 2001. **50**(2): p. 409-16.
- [221] Kang, H. and E.M. Schuman, *Long-lasting neurotrophin-induced enhancement of synaptic transmission in the adult hippocampus*. Science, 1995. **267**(5204): p. 1658-62.
- [222] Rutherford, L.C., et al., *Brain-derived neurotrophic factor mediates the activity-dependent regulation of inhibition in neocortical cultures*. J Neurosci, 1997. **17**(12): p. 4527-35.
- [223] Campenot, R.B., *Development of sympathetic neurons in compartmentalized cultures. II. Local control of neurite survival by nerve growth factor*. Dev Biol, 1982. **93**(1): p. 13-21.
- [224] Chun, L.L. and P.H. Patterson, *Role of nerve growth factor in the development of rat sympathetic neurons in vitro. I. Survival, growth, and differentiation of catecholamine production*. J Cell Biol, 1977. **75**(3): p. 694-704.
- [225] Tsukada, Y.a.S., E, *Neurotropic Factors*. 1992, Tokyo: Japan Scientific Societies Press.
- [226] Liberzon, I. and B. Martis, *Neuroimaging studies of emotional responses in PTSD*. Ann N Y Acad Sci, 2006. **1071**: p. 87-109.
- [227] Badowska-Szalewska, E., et al., *The impact of two mild stressors on the nerve growth factor (NGF) immunoreactivity in the amygdala in aged rats compared to adult ones*. Int J Dev Neurosci, 2016. **49**: p. 6-13.
- [228] Grande, L.A., et al., *Complex regional pain syndrome as a stress response*. Pain, 2004. **110**(1-2): p. 495-8.
- [229] Ruit, K.G., et al., *Nerve growth factor regulates sympathetic ganglion cell morphology and survival in the adult mouse*. J Neurosci, 1990. **10**(7): p. 2412-9.
- [230] Fischer, W., et al., *NGF improves spatial memory in aged rodents as a function of age*. J Neurosci, 1991. **11**(7): p. 1889-906.
- [231] Isaacson, L.G. and S.C. Billieu, *Increased perivascular norepinephrine following intracerebroventricular infusion of NGF into adult rats*. Exp Neurol, 1996. **139**(1): p. 54-60.
- [232] Yan, Q., et al., *Retrograde transport of nerve growth factor (NGF) in motoneurons of developing rats: assessment of potential neurotrophic effects*. Neuron, 1988. **1**(4): p. 335-43.
- [233] Delahanty, D.L., A.J. Raimonde, and E. Spoonster, *Initial posttraumatic urinary cortisol levels predict subsequent PTSD symptoms in motor vehicle accident victims*. Biol Psychiatry, 2000. **48**(9): p. 940-7.
- [234] Dohme MS. *DHHS FOI Control #26444*. Administration, Editor: F.a.D; 1983
- [235] Inc., Y.P., *Summary of Results and Simulations from Study Y101, in L1-79 IND # 128594*. 2019. p. 1-51.
- [236] Rothman, J., E.J. Bartky, and F.P. Halas, *Effect of L1-79 on Core Symptoms of Autism Spectrum Disorder: A Case Series*. Clin Ther, 2019. **41**(10): p. 1972-1981.
- [237] Rothman J, H.P., Bartky E, Weissfeld L, Fischer T, Megerian JT, *A pilot Study of L1-79 in Autism Spectrum Disorder*. 2020: in preparation p. 1-21.
- [238] Lipov, E.G., K. Candido, and E.C. Ritchie, *Possible Reversal of PTSD-Related DNA Methylation by Sympathetic*

Blockade. J Mol Neurosci, 2017. **62**(1): p. 67-72.

[239] Verdi JM, A.D., *Neurotrophins regulate sequential changes in neurotrophin receptor expression by sympathetic neuroblasts*. Neuron, 1994. **13**: p. 1359-72.

[240] Max, S.R., et al., *Nerve growth factor-mediated induction of tyrosine hydroxylase in rat superior cervical ganglia in vitro*. J Biol Chem, 1978. **253**(22): p. 8013-5.

[241] Raynaud B, F.-B.N., Vidal S, Mallet J, Weber MJ,, *Regulation of neurotransmitter metabolic enzymes and tyrosine hydroxylase mRNA level by nerve growth factor in cultured sympathetic neurons*. Development, 1988. **102**: p. 361-8.

[242] Thoenen, H., *Sympathetic nervous system and hypertension*. Verh Dtsch Ges Inn Med, 1974. **80**: p. 124-8.