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Pathogenicity of Endocrine Dysregulation in Autism

Adam J. Swierczynski

University of North Texas

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Abstract

The voluminous daily output of autism research has become increasingly disconnected, existing largely within highly specific subspecialty areas, and lacking cross-disciplinary linkages of context, theory, and findings to inform a unified body of knowledge. Robust syntheses of published research across the fields of psychiatry, cellular and molecular biology, neurology, endocrinology, immunology, behavioral and social sciences, and pedagogy may help clarify and extend current knowledge by guiding more efficient future research efforts investigating underlying causes, developmental divergences, novel treatments, and specific, sensitive biological markers in autism. This synthesis of interdisciplinary research indicates the hypothalamic-pituitary-adrenal (HPA) stress axis may be at the center of an interaction among sex steroids, immune function, signaling protein transcriptions, neurogenesis, and dysregulation of brain structures sending or receiving projections from the HPA stress axis. These interaction manifest observably as a range of sexually dimorphic behaviors and functional limitations often falling within the current diagnostic features of Autism Spectrum Disorder (ASD). The pathogenicity of endocrine dysregulation may serve as a valuable model for developing a cohesive theory of ASD by explaining how the HPA and connected brain areas respond to extreme conditions of dysregulated endocrine signaling to cause symptoms associated with autism.

Keywords: Autism Spectrum Disorder, endocrine, estrogen, immune activation, melanin concentrating hormone

Contents

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1. Introduction

The neuro-developmental disorder of Autism has generated perplexed reactions from the scientific community for nearly 80 years since Leo Kanner[116] first distinguished a set of "feebleminded" (p. 242) children with unique observable characteristics. Kanner borrowed the word 'autistic' from a description of the state of mind observed in patients with schizophrenia who were seemingly lost in their internal world with little consideration for the shared, external world[117] in order to separate this population clinically from other feebleminded children. While autism has been recognized as a unique developmental disorder since Kanner's seminal descriptions, frequent redefinitions and revised conceptualizations of the condition have contributed to subsequent and persisting uncertainties about the nature of Autism Spectrum Disorder (ASD) and the identification of universally effective treatments. Without discrete, objective, and reliable medical diagnostic tools, the meaning of autism remains nebulous, and prone to continuous shifts in its interpretations, especially across gender and culture.

Autism is the focus of rapidly increasing research activities across a widening variety of scientific disciplines. Results are often confounded and have diminished impacts as a result of being viewed through these different competing lenses. Each discipline uses its own paradigms and corresponding language to describe interactions between an organism and its environment. This often leads to very important details being misunderstood, or lost entirely, in translation. This paper synthesizes cross-disciplinary research results in order to develop a theoretical framework to help understand the biopsychosocial underpinnings of ASD.

The medical concept of pathogenicity will be used as the framework of the proposed theory. In its simplest sense, pathogenicity is defined as the ability of an organism to cause disease or harm within its host. The concept of pathogenicity may be used to describe the maximum potential damage a bacteria or virus is capable of inflicting, without consideration of the infected host's ability to combat the microorganism. Throughout this paper, pathogenicity will be used in the context of signaling protein interactions; that is, the maximum damage that may be observed in a biological system when there is dysregulation of the protein or its receptor. Individual differences within organisms which may account for the varying thresholds of tolerance for dysregulation – along with biological redundancies capable of mitigating resulting damage – are not addressed within this paper. We contend there is insufficient research evidence to adequately discuss this factor. The endocrine dysregulation theory of ASD predicates the measurement of such tolerance of dysregulation by operationalizing relevant biological and psychiatric components in the context of behaviors under their modulation.

Because numerous developmental and psychiatric syndromes are comorbid with ASD, researchers (e.g., Gillberg[81] and Volkmar et al.[266]) have concluded that ASD is very rarely a discrete, isolated phenomenon. Learning disability, epilepsy and seizure disorders, motor control problems, attention-deficit hyperactive disorder (ADHD), depression, anxiety, sleep disorders, and gastrointestinal problems frequently occur in tandem with ASD. Consequently, Gillberg and others contend that researchers should investigate relevant factors and causal agents resulting in high rates of similar aberrant functioning across multiple diagnostic indicators of disability, especially if corresponding treatments are to achieve maximum effectiveness.

The convergence of data within cross-disciplinary literature addressing the loci of ASD and overlapping syndromes indicates there may be a shared root in the endocrine system. In

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particular, a self-sustaining positive feedback loop with three initiating points of dysregulation may be responsible for the myriad symptoms observed across ASD and co-morbid disorders (see Figure 1). We believe this proposed theoretical framework is relevant not only to the improved understanding, treatment, and prevention of ASD, but that it can also offer similar insights for other co-occurring syndromes.

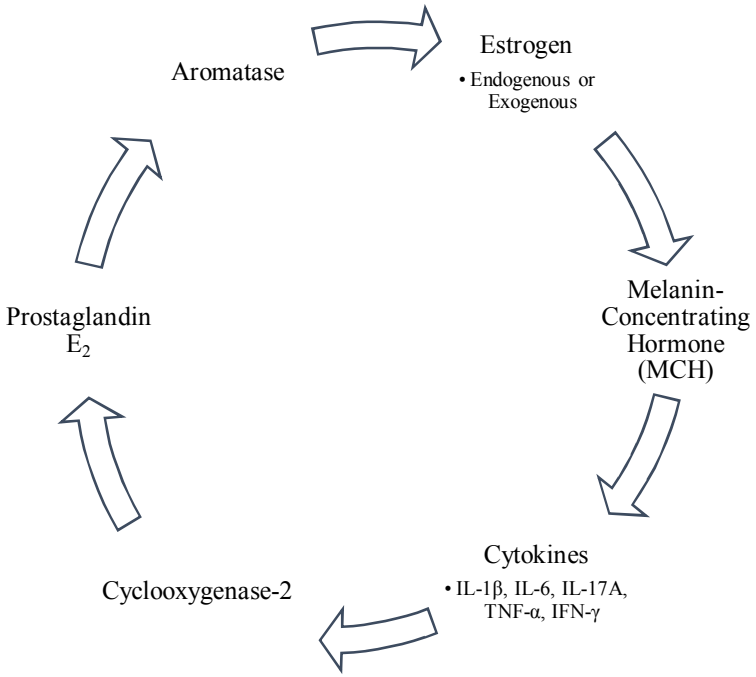

Figure 1. Positive feedback loop of endocrine dysregulation. This endocrine feedback loop is the backbone of understanding the potential biopsychosocial dysregulation observed in ASD.

2. The Consequences of Endocrine Dysregulation

The endocrine system sustains interactions throughout the entire organism in which it is found. Endocrine is an overarching label afforded to signaling proteins – such as gonadal steroids – and many distal interactions caused by the more well-known contributors to this communication system. These communications span the central nervous system (CNS) and many organ systems beyond the sexual reproductive system. These signaling proteins can either cross the blood brain barrier (BBB), or they can be modulated on both sides of the BBB by other

circulating proteins and chemical isomers capable of crossing the BBB to interact with vital receptors. These interactions will be described in more detail below. First, a comprehensive examination of pigmentation must be addressed.

2.1. Systemic Dysregulation of Pigmentation

The results of this review suggest that the pigmentation system may play a previously unaddressed role in the biopsychosocial underpinnings of ASD. Due to the presence of melanin in many sun-deprived tissues[36, 235] such as the inner ear, genitals, and brain tissues, it has been suggested that the primary role of melanocytes – melanin producing cells – and melanin are related to antimicrobial defense and immunomodulation[36].

2.1.1. Neural crest. Biological systems that affect both the skin and brain have a common embryological origin – the neural crest. The neural crest differentiates into many biological systems whose developed forms are rather disparate. During the course of embryonic development the neural crest becomes ganglia of the sensory[15], autonomic[15, 26], and enteric[220] systems, as well as blood vessels, adipose tissue, peripheral nerve sheaths[220], melanocytes, connective tissue[15, 26, 220], membranous bone[26, 220], and endocrine cells[15, 26]. Early developmental insult to the neural crest has lasting and cascading consequences spanning the whole body.

2.1.2. Neuromelanin. There are two known forms of melanin in mammals: Eumelanin is responsible for brown and black pigmentation, while pheomelanin is responsible for reddish and yellowish colorings[235]. Neuromelanin is typically observed as a pheomelanin core with a eumelanin surface[99, 235]. Pheomelanin is generally considered to be a weaker neuroprotector leaving mammals with lighter skin and hair coloration more susceptible to environmental insult as a result of higher pheomelanin expression needed for the lighter coloration[99]. Eumelanin has been difficult to study due to its insolubility and chemical resistance, while pheomelanin is easily

dissolved in alkali media[235]. These factors may contribute to the efficacy of neuromelanin in performing its roles in the brain.

In the human brain the hypothalamus, frontal lobe, cerebellum, and substantia nigra – named for its dark coloration – are able to produce neuromelanin[234] in the course of prostaglandin (PG) production. PG production is observed in the fetal pre optic area (POA) when the hypothalamic-pituitary-adrenal (HPA) axis is activated via glucocorticoids[274]. Pre- and neonatal disruption of the HPA axis and related pathophysiological consequences will be a recurrent theme in this review.

Normal functioning of neuromelanin includes the regulation of electrical signaling by acting as a threshold switch. Thus, as a semiconductor, neuromelanin has the ability to prevent signals with too low a voltage from inducing neuronal transmission[161]. Other noted functions of neuromelanin include the chelation of heavy metals from the brain[234]. This affords insight into a role for melanin in the formation of neurodegenerative disorders. The trapping of heavy metals within neuromelanin, particularly iron, has been implicated in Parkinson's disease, ostensibly by reducing the efficacy of neuromelanin to perform as a threshold switch[99, 161, 234, 235]. Selective degeneration of the substantia nigra has been observed in Parkinson's disease[99, 234]. Additionally, brains of patients with Rett's syndrome have paler substantia nigra, which has been attributed to heavy metals' ability to induce depigmentation[234]. It should be noted that mercury is the most commonly used skin-lightening compound found in cosmetics because of its role in countering the aggregation of melanin in human tissue[82]. With neuromelanin's role as a threshold switch, gating transmissions with too low a voltage, the loss of neuromelanin may explain the high rates of epilepsy observed in females with Rett's syndrome[176] as well as individuals within the broader ASDs[106, 263].

2.1.3. Tuberous Sclerosis Complex. Tuberous Sclerosis Complex (TSC) is a neurological disorder where there are observable patches of depigmented skin[183, 182]. TSC is characterized by neurological manifestations such as infantile spasms, epilepsy, cognitive disabilities and autism[182]. Reports indicate that as high as half of the population with TSC has a concurrent autism diagnosis, with approximately one in nine persons receiving a comorbid diagnosis of autism and epilepsy[231]. In many persons with TSC, a lack of melanin results in hypomelanic macules ("ash leaf spots") which are white or lighter patches of skin that may appear anywhere on the body. If pigmentation is disrupted throughout the whole body, as hypothesized, atypical neuromelanin distribution at neuron sheaths, along with endocrine disruption, may be assumed to play a significant role in the overall expression of TSC.

2.1.4. Sexual dimorphism of pigmentation. Skin pigmentation has previously been theorized to have been under the influence of overt sexual selection[109]. Anthropological examination has conferred that there is a biological root in the sexually dimorphic expression of skin pigmentation. In every geographic location – when examining people of the same racial background and degree of sun exposure – women are universally lighter skinned than males[109]. Theoretical speculation based on these results infers that women have a higher need to metabolize vitamin D and calcium to support offspring both during gestation and lactation. Possibly, less expression of melanin allows for enriched acquisition of vitamin D from sunlight.

2.2. Melanin Concentrating Hormone Dysregulation

Melanin-concentrating hormone (MCH) was named for its notable ability to draw melanin back into the melanocyte resulting in the visible reduction of pigment, as observed in lower animals such as fish[272]. Due to the shared embryonic origin of critical parts of the CNS and the pigmentation modulating systems of vertebrates, there is a significant overlap between

the two. This overlap is observed in the form of the melanocortin system and its opposing biological network, the MCH system.

2.2.1. MCH system. Despite its omnipresence and potentially important interaction capabilities, MCH is underrepresented in scientific discussions of behavior and psychiatry. The specific distribution of the MCH system leaves MCH poised to be the central signaling protein in the body driving the possible development of cognitive and emotionsl dysfunction. The key observable features of the MCH system are MCH, MCH receptor 1 (MCHR1), MCH receptor 2 (MCHR2), and their protein coding instructions – called mRNA.

2.2.1.1. *MCHR1*. MCHR1 was first identified as a G-protein coupled receptor with mRNA expression found in overlapping locations throughout both rat and human brain structures. MCHR1 responds exclusively to the signaling protein MCH[228]. Areas where observed distribution of MCHR1 has been reported include: pituitary[210], olfactory regions[43, 143, 196, 210], basal forebrain[43, 196], midbrain[43, 130], hindbrain[43], cerebral cortex[27, 43, 104, 130, 143], hypothalamus[43, 130, 143, 196, 210], thalamus[43, 130, 143], substantia nigra[43, 130, 210], hippocampus[27, 43, 131, 196], locus coeruleus (LC)[210], amygdala[27, 43, 104, 196, 210], spinal cord[143], adipocytes[34], and bone marrow[139]. The distribution of MCHR1 shows strong evolutionary conservation across all mammals observed[43, 130]. Due to the widespread locations of MCHR1, inferred functions could include the regulation of: energy balance and feeding[143], generalized arousal[143], autonomic control[143], sensorimotor integration[130, 143], regulating emotions such as fear[196], anxiety[100, 196], and aggression[100], passive avoidance[100], memory regulation[196], sensory gating[100], epileptiform activity[100], and immune modulation[139, 258, 259].

2.2.1.2. *MCHR2*. MCHR2 has overlapping mRNA expression with MCHR1, but it is only seen in higher mammals, including dogs, ferrets, and primates[243]. The amino acid sequence

of both MCH receptors are identical[268] indicating MCHR2 also responds exclusively to MCH. Expression of MCHR2 is most heavily observed in the cortical regions of the brain[9, 268]. In addition to being expressed in the cerebral cortex[9, 104, 173, 243, 268], MCHR2 mRNA is also seen in the amygdala and hippocampus[9, 104, 173, 243, 268], corpus callosum[9, 173], hypothalamus[243], thalamus, caudate nucleus, frontal, temporal, and occipital lobes[9], and nucleus accumbens[268]. Again, given the numerous locations of MCHR2, inference of emotion and memory regulation[173] in combination with energy balance and food intake[268] have been suggested to be under the influence of this receptor.

2.2.1.3. *MCH*. MCH is an amino acid synthesized in the enteric[284] and central nervous system – predominately in the lateral hypothalamus and zona incerta[196, 210]. The amino acid sequence for human MCH is identical to rat[100, 196, 210] and mouse[100, 196] MCH. As a result, these models have been used almost exclusively to study the effects of MCH antagonization and agonization. However, the results of these studies may only indicate what happens to a mammal when MCHR1 is the exclusive target, since lower mammals do not express MCHR2. Since humans have both MCH receptor types it is difficult to infer how MCH influences human emotions and behaviors based on these rodent models of behavior. Humans with electrodes implanted in the brain as part of pre-surgical diagnostic evaluations enabled the discovery that MCH levels are lowest while humans experience strong emotion, social interaction, and physical pain. MCH levels also follow a diurnal rhythm where MCH is highest at sleep onset[29]. Experiencing pain being the point of lowest MCH levels might imply the function of self-injurious behavior in individuals with ASD is to reach higher levels of psychological salience by reducing MCH levels. Non-suicidal self-injury (NSSI) – unrelated to depression or emotional dysregulation – occurs at significantly higher rates in individuals with ASD than typically

developing individuals, and women with ASD engage in NSSI at significantly higher rates than males[157].

2.2.2. Sexual dimorphism of MCH. Expression and interaction in the MCH system has been shown to be sexually dimorphic. In humans, females have higher levels of MCH than males[76]. A positive correlation between fat mass and MCH levels has also been observed[34, 76, 101]. Highly dense MCHR1 expression has been seen on the ovaries, while only sparse expression in the testes has been reported. Conversely, MCHR2 has only been observed in the testes, with no expression found in the ovaries in human tissue samples[173]. When the food supply for male mice was supplemented with the hormone Estradiol (E_2), hypothalamic MCH expression increased while proopiomelanocortin (POMC) expression decreased[253]. The behavioral effects of MCH injected into the lateral ventricle – as measured by increased food intake – were weaker in female rats than male rats, and a control group of ovariectomized rats showed that estradiol benzoate treatment reduced these behavioral effects of MCH injection[217]. Because fat mass is a sexually dimorphic trait where females typically have higher Body Mass Index (BMI) than males, MCH levels rising in male mice given E_2 injections along with muted behavioral effects of MCH by estrogen could be interpreted to mean there may be important relationships between female physiology and MCH expression, as well as potentially observable protective interactions between estrogen and MCH.

2.2.3. Behavioral inhibition. Behavioral inhibition (BI) was initially studied in Caucasian children by Rosenberg and Kagan, who operationally defined BI as "The temperamental quality inhibited connotes an initially restrained and affectively subdued reaction to new people, places, or objects[205] (p. 754)." Various dysfunctional levels of this behavioral phenotype is inherent in the diagnosis of individuals with ASD, who are often hyporesponsive to

both social and non-social stimuli[16]. Further investigation and replication studies concluded that in young children, having blue eyes was positively correlated with BI[204, 205, 207], with females being more behaviorally inhibited than males. However, this observed correlation weakened as the participants neared age nine, and no correlation between eye color and BI was observed in children nine years old and older[207]. The Rosenberg and Kagan suggested a contributing role for the melanocortin system in the origin or regulation of BI, via α-melanocyte stimulating hormone (α-MSH)[204, 205], POMC[205], and areas of the brain such as the HPA axis, amygdala, reticular activating system, and sympathetic nervous system[204]. For example, in both rats and mice bred to display BI, MCH mRNA was higher in the hypothalamus than in control populations bred to display high behavioral responsiveness, with the BI mice showing more depressive-like behavior[75]. Mice with MCHR1 genetically deleted both explored novel environments and engaged in social interactions with strange mice (intruders)[206] compared to controls. These animal models establish a possible link between MCH, the HPA axis, and BI while depicting behaviors that resemble some of the core features of ASD.

To further exemplify the hypothesized link between the HPA and BI, the relationship between BI and corticotropin-releasing hormone (CRH) needs examination. In response to stress, the hypothalamus releases CRH which triggers the release of adrenocorticotropic hormone (ACTH) once it binds to CRH receptors in the pituitary, and ACTH acts on receptors in the adrenal cortex to release glucocorticoids – such as cortisol[201]. Arginine-vasopressin (AVP) is cosecreted with CRH, and AVP potentiates the actions of CRH, facilitating the release of ACTH[140]. The glucocorticoids bind to glucocorticoid receptors in various tissues – particularly ones regulating the HPA axis to reduce the secretion of CRH and ACTH[97]. Glucocorticoids also act on AVP to aid in the restraint of the HPA axis stress reaction[97]. High levels of cortisol in BI

children have been interpreted to indicate that CRH plays a direct role in Rosenberg and Kagan's concept of BI[226]. Additionally, variations of a gene responsible for CRH have been associated with the BI temperament in humans[232, 233]. Further support for the role of CRH in mediating BI was observed when lateral ventricle injections of CRH into baby rhesus monkeys caused BI[115]. CRH receptors have been found in the hippocampus, septum, amygdala, neocortex, thalamus, hypothalamus, cerebellum, and pituitary gland[226] – overlapping with the locations where MCH receptors are expressed in the brain.

2.2.4. Neurological dysregulation. Because the HPA axis is often considered to be the center of patterned behavior for escape and avoidance of stressors and novelty, further inquiry into interactions with other brain areas is warranted. MCH projections extend from the hypothalamus to areas of the brain that govern arousal, reward, emotion, anxiety, fear, memory, and sensorimotor integration. In concert, the influence of MCH may shape an organism's ability to construct adaptive behavior during the cognitive course of evaluating past environmental responses, the consequences of producing these responses, and the contextual appropriateness of any given response to current environmental stimuli.

2.2.4.1. *Melanocortin system dysregulation.* The melanocortin and MCH systems interact in both complementary and opposing manners dependent upon which of the melanocortin signaling proteins are being observed. The melanocortin system has three classes of signaling proteins – MSH, agouti-related protein (AgRP), and ACTH. These proteins interact at five receptors which regulate pigmentation, steroidogenesis, energy homeostasis, inflammation, and exocrine gland function[186]. POMC is the precursor to ACTH, β-endorphin, and α-, β-, and γ-MSH[186]. Given that experiencing physical pain lowers MCH levels, it is proposed that the biological response to quell pain with endorphins results in increased

transcription and release of POMC. The HPA axis is the primary point of interaction for the melanocortin system, with tertiary influences throughout the body.

2.2.4.1.1. *AgRP.* AgRP expression is observed in the hypothalamus, subthalamic region, and adrenal cortex with its primary neurological role in the hypothalamus[73]. The presence of AgRP in the brain is modulated by two of the signaling proteins identified in the proposed endocrine dysregulation feedback loop. AgRP expression in the hypothalamus is regulated by the ratio of activity of estrogen receptor α (ERα) and estrogen receptor β (ERβ), with a surplus of ERβ activity in the hypothalamus upregulating AgRP[252]. MCH activity provokes release of AgRP as well[101]. It is unknown at this time if estrogen increases AgRP independently of MCH or as a downstream result of increasing the expression of MCH. Reported cognitive effects of AgRP show a positive correlation between levels of plasma AgRP and deficits in cognitive flexibility[219].

Aside from HPA axis interactions, AgRP plays other important roles in α-MSH activity and expression. α-MSH binding to melanocortin receptor 1 is antagonized by AgRP resulting in the blockade of eumelanin production and switching to pheomelanin production[186, 227]. Energy homeostasis is another realm where AgRP opposes the anorectic effects of α-MSH during fasting, while also inhibiting POMC transcription[69]. Blockade of α-MSH and decreasing its transcription contribute significantly to the behavioral effects of AgRP much in the same manner in which MCH opposes the behavioral effects of α-MSH.

2.2.4.1.2. *MSH.* The most studied and influential of the hormones in this class is α-MSH. Named for its ability to stimulate the melanocyte to release melanin and increase pigmentation, it generally produces effects opposite of MCH in vertebrates. MCH and α-MSH directly oppose

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each other's effects through the activation of their respective receptors, which appears to be the primary interaction between these two signaling proteins[86, 100, 121, 162, 212].

α-MSH may have a beneficial role in modulation of attention and sensory gating. Men with mental retardation were given intravenous MSH/ACTH 4-10 – a section of POMC that ultimately reduces to α-MSH – and testing showed that fewer errors and higher attention were observed among these men compared to the control group[214]. This increase in cognitive function and ability to adaptively respond to environmental demands may drive NSSI in order to suppress MCH by distally increasing ACTH and α-MSH. Lateral ventricle injection of α-MSH and MCH into rats respectively improved and worsened sensory gating with regard to auditory stimuli as noted by shifts in evoked potential recorded with implanted microelectrodes[162]. Systematic review of MSH has led to the proposed behavioral role for these signaling proteins as mediators in the selection and filtering of information transmitted through sensorimotor processing systems[22].

While some overlap has been reported on the anxiogenic nature of α-MSH and MCH to generate anxiety[86] there may be a difference in the function of the anxiety. α-MSH may facilitate anxiety as part of the process for priming the organism for action to adapt to the source of the anxiety, whereas MCH may facilitate anxiety as part of the flight or freeze response to stress. The possible role MCH plays in BI has been discussed, yet the role of α-MSH may equally oppose such an influence. When α-MSH was administered to rat pups between two and seven days old, male rats grew into adults displaying significantly more "gregariousness" (p. 298) than females treated with α-MSH, and both male and female control populations[21]. Human fetal tissue expresses more α-MSH than adult tissue[229, 261] and this has been interpreted to mean α-MSH plays a significant role in the development of the male-differentiated brain[229], particularly

the hypothalamus[261]. This concept is supported by findings that α-MSH enhances biological responses to androgens in rats given supplemental α-MSH throughout the first five weeks of life. These rats showed responses that were neither observed in rat pups receiving doses of α-MSH for shorter durations/intermittent administration nor in adult rats given five weeks of α-MSH supplementation[250]. Even an intermittent disruption of α-MSH – due to dysregulated expression of MCH – may have serious developmental consequences in the context of social behavior.

An age dependent seasonal rhythm – but no diurnal rhythm – of α-MSH was observed in adult human males and females aged 20-40 years old that diminished as age increased; during the summer months circulating α-MSH levels were higher than in winter months suggesting ultraviolet (UV) exposure regulates expression of α-MSH[7]. Early exposure to α-MSH may prime vertebrates to behave in a manner consistent with exploration and adaptation to stress, while similar exposure to MCH may prime vertebrates to avoid and withdraw in response to stress; summer months are marked with environmental abundance of resources enabling more energy expenditure while winter months require more conservation. Thus, being born at a specific time of year may have some influence on the temperament of the organism.

As summarized above, findings regarding the biopsychosocial effects of α-MSH seem to converge on a common point: α-MSH plays two critically important roles in normal functioning, including inhibition of pro-inflammatory cytokine production[73, 139, 275], and the facilitation of learning and memory[24, 187], motivation[24], and attention[22, 24]. These areas of influence overlap with what is known about MCH. The opposing effects of MCH and α-MSH offer insight into the regulation of emotions and behavior in a greater environmental context.

2.2.4.1.3. *ACTH*. This signaling protein of pituitary origin is under the dichotomous influence of MCH and α-MSH. Receptors for ACTH are found almost exclusively in the adrenal

cortex[186]. ACTH appears to complement the function of α-MSH as noted by ACTH injections in humans leading to increased skin pigmentation[94]. This complementary influence may stem directly from ACTH being a precursor to α-MSH. ACTH has a diurnal rhythm with its peak occurring three hours before onset of darkness – the point in the cycle where MCH also has the strongest effects on ACTH – suggesting a positive correlation between duration and intensity of light exposure and ACTH levels[28]. MCH exerts inhibitory control over ACTH[153, 168] while α-MSH stimulates ACTH secretion[153]. With α-MSH being a derivative of ACTH, it is possible that α-MSH upregulates POMC – the amino sequence from which ACTH is derived.

There are behavioral effects and potential developmental processes modulated by ACTH which overlap with α-MSH functioning as well. The key role of mediating processes responsible for selecting and filtering data moving through information processing systems has been attributed to ACTH[22]. Learning and memory regulation[24] has been suggested to be another common role with α-MSH. With ACTH showing the capability to stimulate testosterone production in mouse neonates, but not at later stages of life[113], this may indicate a shared role in sexual differentiation as well.

Overlap of ACTH with the endocrine system may very well be a two-way street in vertebrates. While ACTH may stimulate testosterone production in rat pups, supplementation of testosterone in human males who have been surgically castrated or who were considered hypogonadal show increased pigmentation production in the skin that fades when testosterone supplementation is withdrawn[95]. A possible explanation is that POMC is being upregulated by testosterone, with POMC eventually being reduced to α-MSH, which directly influences the production of melanin at the melanocyte.

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2.2.4.2. *Glucocorticoid dysregulation*. Glucocorticoids act on the HPA axis to restrain activity after stress response[226]. This signaling protein of adrenal origin[186] is under the dichotomous influence of α-MSH and MCH. This regulation of glucocorticoids occurs with α-MSH increasing glucocorticoid levels by stimulating ACTH secretion, and MCH reducing glucocorticoid levels by inhibiting ACTH secretion[153]. After HPA axis stress response, glucocorticoids act to reduce transcription and release of CRH and POMC[33]. However, chronic activation of the HPA axis leads to glucocorticoid resistance[33, 286] as glucocorticoids transcriptionally down-regulate glucocorticoid receptors[164]. Excess sex hormones (both estrogen and testosterone) can trigger a hypothalamic negative feedback mechanism where glucocorticoid release suppresses gonadotropin-releasing hormone to lower sex steroid levels[273]. Glucocorticoid resistance could lead to impaired restraint of sex steroids in the brain. Another notable side effect of glucocorticoid resistance is obesity[101].

Within the framework of the HPA axis, glucocorticoids exert strong metabolic control. As part of the fight or flight response[33, 273], this adrenal signaling protein increases glucose availability and decreases glucose sensitivity in order to mobilize behavioral responses to stress[33]; chronically elevated glucocorticoid levels increase the risk of developing insulin resistant diabetes mellitus. In further aid of energy mobilization, glucocorticoids trigger protein breakdown, glutamine synthesis, and lipolysis in order to maintain an increase in energy availability. Additionally, glucocorticoids have been observed to act on the hypothalamus to stimulate MCH mRNA[100] with the likely purpose being a delayed increase of MCH levels so as to induce increased appetite for recovering from the rapid depletion of energy stores. With MCH also inhibiting ACTH secretion, this may be yet another means by which glucocorticoids exert negative feedback on the HPA axis.

Capable of exerting a direct effect on gonadal function in the ovaries, testes, hypothalamus, and pituitary[273], the behavioral effects and expression of glucocorticoids may be sexually dimorphic. Notably, there is a positive correlation among glucocorticoid resistance, body fat mass, and MCH. Additionally, during the luteal phase of the menstrual cycle – where estrogen and progesterone levels are higher – decreased glucocorticoid sensitivity was observed in human females[33]. With females showing greater immune response than males, the recruitment of the HPA axis to attenuate or resolve pro-inflammatory immune response via glucocorticoids' immunosuppressive[33] and anti-inflammatory[33, 271] actions, may sooner lead to glucocorticoid resistance sooner in females than males. Other notable reproductive-related interactions of glucocorticoids are infertility and bearing offspring with permanent HPA axis dysregulation due to maternal exposure to glucocorticoids resulting from chronic stress[273].

2.2.4.3. ***Calcium ion channel interference.*** Calcium ion channels and MCH activity modulate each other in a reciprocating manner. Too little activity at, or expression of, MCHR1 leads to increased potentiation in calcium ion channels in MCH neurons of the lateral hypothalamus, triggering increased release of MCH[91, 225]. In a natural state, this serves to ensure that an appropriate amount of inhibitory control is maintained throughout key areas of the brain. MCH activity in the lateral hypothalamus leads to decreased glutamate and γ-aminobutyric acid (GABA) receptor activity[74, 101] by depressing calcium ion currents at the synapse[74]. Glutamate and GABA are the main excitatory and inhibitory neurotransmitters, respectively[194].

2.2.4.4. ***Dysregulated inhibition and excitation.*** One of the more important roles for excitation and inhibition is regulating the level of arousal in response to environmental stimuli. Incoming sensory information results in excitation followed by inhibition so as to demark a clear ending to a discrete sensory experience[108]. Failure to initiate a proper beginning to or a clear

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ending of these sensory events leads to inability to distinguish relevant environmental stimuli and provide adaptive responses.

The paradigm of an environmental awareness which prompts adaptive response is generally referred to as sensory gating. With MCH exerting control over both excitation and inhibition through modulation of glutamate and GABA activity, respectively, it can be assumed that the most important emotional and behavioral influences of MCH stem from impaired sensory gating. The exogenous introduction of α-MSH and MCH into the organism resulting in the opposing control over sensory gating has been highlighted so far, but understanding the role of endogenous MCH in sensory gating impairment is necessary as well. Higher MCH mRNA in the hypothalamus of rats was positively correlated with sensory gating impairments, and the blockage of MCH signaling reversed these deficits[47]. MCH neurons are capable of both feedforward and feedback interactions with glutamate and GABA; capable of releasing both but only releasing GABA in response to glutamate activation, MCH neurons exert a predominately inhibitory effect[44]. With the hypothalamus sending and receiving projections to much of the brain, this central interruption of excitation and inhibition has widespread implications.

2.2.4.4.1. *N-methyl-D-aspartate receptor dysregulation*. N-methyl-D-aspartate (NMDA) receptors are one of many glutamate receptors in the brain responsible for neuronal excitation[108]. MCH is capable of modulating calcium ion levels in the NMDA system[256], which may explain for MCHR1 activity modulating NMDA transmissions[184]. When mice had MCHR1 genetically deleted, NMDA responses and receptors were found to be reduced in the CA1 region of the hippocampus[3]. It should also be noted that while MCH in the hypothalamus was increased in mice bred to demonstrate BI, the expression of MCHR1 was lower in CA1 of the hippocampus[75]. This interruption of excitation may serve to impair arousal in the context of reducing the

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perceived significance of environmental stimuli with possible results being impaired long term potentialtion.

2.2.4.4.2. *Serotonin dysregulation.* Serotonin (5-HT) plays a role in the excitatory tone of the brain. 5-HT receptor activation increases the release of glutamate onto layer V pyramidal cells[4]. It has been suggested that MCH plays a role in the modulation of amine release resulting in the distal modulation of 5-HT[100]. Additionally, melanocytes – the primary source of melanin production in mammals – are capable of secreting 5-HT[36]. With MCH reducing 5-HT, this is yet another example of how MCH subverts the functional redundancy responsible for maintaining balanced excitation and inhibition. In a developmental context, 5-HT plays an important role in neural cell migration, proliferation, and differentiation as well as neurite outgrowth, leading to the supposition that dysregulation of 5-HT may underlie the pathogenesis of autism[48].

While MCH may directly lower 5-HT levels, distally, the role of MCH in inflammatory responses of the immune system may lead to increased 5-HT synthesis. Several pro-inflammatory cytokines have been linked to 5-HT level increases in the hypothalamus, hippocampus, and cortex due to their enzymatic regulation over the process of tryptophan being converted to 5-HT[11]. If 5-HT is able to promote neural inflammation, this may establish a link between exceeding basal 5-HT signaling and neurodegenerative symptoms such as cognitive decline, changes in appetite and metabolism, as well as affect.

2.2.4.5. ***Consequences of HPA axis dysregulation.*** Aberrant function of the HPA axis has the potential to disrupt essential processes throughout much of the brain. Response to stress, changes in available light in the context of both diurnal and seasonal cycles, sex steroids, and inflammation are all potential catalysts for the dysregulating influence of MCH. With the hypothalamus being the primary producer of MCH in the brain, given the known distribution of

MCH receptors throughout the brain and body, attention to the potential cascade of disrupted functions stemming from one site may offer insight into the onset and maintenance of psychiatric and developmental disturbances with ASD being the most severe psychiatric consequence.

2.2.4.5.1. *Thalamocortical dysregulation.* The thalamocortical system synchronizes activities of the thalamic and cortical neurons[114]. Inhibition is vital in the process of the thalamus bundling and interpreting sensory information from multiple cortical regions to facilitate the formation of a uniform perceptual experience of the external environment[151, 165]. Disruption of organization and timing contributes to neurological and psychological disorders[151] such as obsessive compulsive disorder (OCD)[165]. While GABA has a largely inhibitory role, binding to $GABA_B$ receptors of the thalamocortical system has been shown to prime the thalamocortical cells for burst firing through calcium ion channel interactions[54]. Extreme inhibitory control or lack of inhibitory control of the thalamocortical circuit has been proposed to be at the center of obsessive-compulsive behaviors[165]. Excessive inhibitory control may induce a state of repeated burst firing, while a lack of inhibitory control would also subvert a cessation of thalamocortical firing, and in both circumstances the ability to correlate sensory events into a continuous reality would be stifled.

2.2.4.5.2. *Cortical dysregulation***.** In the first few years of life, the maturation of the cortical and subcortical neural substrates support visual attention, alertness and orientation, executive attention, and sustained attention[17]. In the cortex, the role of excitation and inhibition makes up the primary means by which sensory information is prioritized and attended. GABAergic inhibition is the primary mode of regulating the function of cortical neurons[108], with most of the local circuit neurons in humans being GABAergic interneurons[77]. Circuits which respond to both GABA and glutamate are responsible for making sure the neurons are neither too

inhibited nor excited in order to prevent presentations of comatose or epileptiform activity, respectively[108]. With the cortical regions of the brain having the highest concentrations of MCH receptors, aberrant MCH signaling could contribute to extreme oscillation between hyper- and hypo-responsiveness within the cortical networks. This is exemplified by the intra-layer communication in the cortex where inhibition of layer II/III of the cortex can cause excitation in layer V[108].

An intersection of learning disabilities, cortical dysregulation, and hypopigmentation has been reported. One study found higher rates of expression of learning disabilities among children with blond hair[222]. In a more specific inquiry, stuttering severity was strongly correlated with blue eyes and blond hair, with the authors implicating the cortex as the key point of dysregulation responsible for the communication impairment[46]. When investigating rates of autism, hypopigmentation was found to be overrepresented among patients with autism living in Australia[98]. In a developmental context, the increase and decrease of GABA release in pyramidal neurons of layers II/III in the early postnatal mouse cortex led to the respectively increased or decreased formation of inhibitory (gephyrin puncta) and excitatory (dendritic spines) circuitry through interactions with $GABA_A$ receptors and calcium ion channels[178]. With MCH capable of arresting GABA receptor activity via calcium ion currents at the synapse, an overexpression of MCH may disrupt the development of essential cortical circuitry – pyramid neurons – not only in layer II/III but also in layer V.

2.2.4.5.3. *Locus coeruleus dysregulation.* Rosenberg & Kagan directed attention to the LC for its potential contribution to BI due to its visible saturation of neuromelanin[204]. The LC optimizes the trade-off between exploiting known reward sources and exploration for new rewards in a changing environment through the utilization of sensory data from the cortical

projections[12]. Responding to reward and punishment[218], the LC is the sole source of noradrenaline required to support working-memory tasks and selective attention[25, 218]. Under direct influence of glutamate, GABA, 5-HT, and CRH, the LC also modulates stress and arousal-related processes[25] in combination with sensory information processing[25, 84]. The amygdala sends CRH projections to the LC[25], and the LC is also able to restrain CRH[226].

Disruption of the LC has been linked to disorders that are co-morbid with ASD, including schizophrenia[12], depression[12, 13], anxiety disorders[12, 13], sleep disorders[13], and ADHD[13]. fMRI has shown the LC to be the primary point of activation in response to social gaze[224]. Genetic deletion of MCH signaling in mice led to decreased inhibitory input of MCH neurons onto the LC, producing more wakefulness[244]. MCH has been proposed to dampen arousal and promote sleep via inhibition of synaptic release of GABA and post-synaptic action of GABA in LC neurons[58]. With MCH being able to distally stimulate 5-HT production through inflammatory cytokine responses, MCH presents a paradoxical situation where aberrant MCH signaling could result in either a hyper- or hypoactive LC dependent upon degree of dysregulation.

2.2.5. Interplay with immune system. Melanin and its modulatory hormones play a central role in the immune system. Melanocytes are capable of secreting cytokines[36], potent immune signaling compounds which modulate inflammatory responses. MCHR1 and MCHR2 are found in human bone marrow[139] with implications that immune responses may be triggered by MCH signaling. α-MSH is capable of down-regulating inflammatory cytokines – most of which are in a group known as interleukins (ILs) – such as IL-1, IL-2, IL-6, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ)[139]. Th2 immune cells express the gene for pro-MCH – a prohormone which acts on the hypothalamus to produce MCH – and is suggested to be the link between MCH and allergic-inflammatory diseases such as asthma[213]. While considering

allergic interactions, it is worth noting that histamine receptors are found on MCH neurons[189] inhibiting MCH activity, and histamine stimulates melanin production[36] illustrating additional association of the MCH system to allergic response. With MCH generating nearly completely opposing effects to α-MSH, the presence of MCH receptors in bone marrow, and T helper (T_h) cells being capable of transcriptionally increasing the presence of MCH, it can be inferred that MCH modulates inflammatory responses to produce an increase of the cytokines IL-1, IL-2, IL-6, TNF-α, and IFN-γ. This has been observed to be the case in animals, where MCH was genetically ablated was correlated with lower mRNA expression for IL-1β, IL-6, TNF-α, and IFN-γ[139].

Of key importance is the potential for a positive feedback loop to occur between MCH and the pro-inflammatory cytokines – both to halt and antagonize the effects of MCH receptors. In the human brain IL-6α receptors have been shown to be exclusively expressed on MCH neurons in the hypothalamus, and implications are that IL-6 opposes the orexigenic effects of MCH to suppress fat mass[223]. With IL-6 transcriptionally regulated by MCH and the potential for IL-6 to inhibit MCH, another purpose may be to prevent immune activation from becoming pathological. To that effect, MCHR1 was identified as an auto-antibody site of interaction in patients with vitiligo – an auto-immune disease resulting in loss of skin pigmentation[120, 121]. The primary antibody found to interact with the MCH receptors was identified as IL-17A, which, aside from halting melanin production, also induced production of IL-1β, IL-6, and TNF-α in skin cells[62]. While IL-6 may intermittently inhibit MCH neurons (else the organism die of starvation), it would appear IL-17A triggers a lasting activation of MCH receptors, as loss of pigmentation in vitiligo seems to be permanent. This illustrates that the potential immune interactions with the MCH system are capable of exerting a widespread effect on the organism.

2.3. Cytokine Dysregulation

MCH being linked to the transcription of inflammatory cytokines is not the only point at which neural crest derivatives interact with the immune system. Lipopolysaccharides (LPS) are capable of activating immune responses in melanocytes, which includes the release of cytokines[36]. The skin is one of the first points of defense in the control of pathogenic microorganisms. The organ systems first in line to defend the host from the environment – such as the skin, lungs, and intestines – are those with the highest concentrations of IL-17 producing cells. Subsequently, research using mouse models has concluded that aberrant gut flora can trigger the production of IL-17a, resulting in neurological and behavioral dysregulation in offspring[123]. LPS exposure is also reported to increase IL-1 receptors on AgRP neurons with inflammatory signaling, namely IL-1β, decreasing AgRP secretion yet increasing AgRP mRNA expression[221]. This example is one of many where positive feedback loops initiated by exogenous stimuli may lead to pathological symptoms being expressed over time.

2.3.1. Positive feedback loops. Of particular concern in this pattern of inflammation is the means by which inflammatory cytokines behave synergistically and up-regulate expression of each other. To understand how a day one increase in IL-6 has the potential to dysregulate cytokine expression and neurological development this feedback loop must be examined. IL-1β and IL-6 act on T_h cells in the bone marrow microenvironment, triggering differentiation of the T_h cells to T_h 17 cells[55, 282]. These T_h 17 cells are responsible for the production of IL-17A, IL-17F, IL-21 and IL-22 which all play important roles in inflammation and autoimmune disease expression[282]. IL-17A promotes the production of IL-1β, IL-6, IL-8, and IL-23 with IL-1β, IL-23, and TNF capable of inducing rapid secretion of IL-17A[55]. It is possible that MCH may cause a distal increase in IL-17A expression via its transcriptional regulation of IL-1β, IL-6, and TNF.

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It should not be ruled out that IL-17A activating MCH receptors may afford the same transcriptional up-regulation of these inflammatory cytokines.

2.3.2. Astrocyte and microglial cell dysregulation. Microglial cells are derivatives of bone marrow, capable of producing IL-1, IL-2, IL-6, TNF-α, and IFN-γ which act on the HPA axis[170]. One notable effect of cytokines on the HPA is cytotoxic damage to the hypothalamus, resulting in infertility when cytokine load blocks luteinizing hormone and subsequent ovulation[170]. Estrogenic activity on microglia producing sustained activation is reportedly the cause of hypothalamic degeneration[170]. In another neurodegenerative disease – multiple sclerosis – IL-1β and IL-6 overexpression is proposed to lead to astrocytes expressing IL-17[255].

2.3.3. Sick behavior. Cytokines exert control over the HPA axis for evolutionarily sound purposes. These sick behaviors help to facilitate the host's survival of an infection – via generation of fever from pyrogenic cytokines, for instance – while also serving to preserve the species by triggering asocial behaviors. Cytokine driven behaviors seen in ASD, such as depression, altered sleep patterns, and social withdrawal[180] serve to afford a drive to isolate and rest in neurotypical populations so as to increase the likelihood of warding off infection while also preventing the spread of infection to the community at large.

When signaling becomes too frequent or in too great a magnitude, receptors for any signaling protein are typically down-regulated to restrain prolonged stimulation of this pathway. Contradiction to the assumed down-regulation of its own receptor has only been observed for IL-1β receptors where both IL-1β and IL-6 have been shown to up-regulate expression of IL-1β receptors. IL-1β and IL-6 have been shown to increase AVP, which stimulates the release of ACTH[276]. In this state, HPA axis activation leads to the distal release of both IL-1β and IL-6

which act on the HPA axis to sustain activation. Prolonged activation of these cytokines leads to overstimulation and neurodegeneration of these areas.

2.4. Aromatase Dysregulation

Aromatase regulates the effects of estrogen on the brain. Cerebral inhibition of aromatase has been shown to abolish brain-specific estrogen action[14]. With aromatase being detectable in the human brain starting at the fourth gestational month, followed by a steady increase over the last trimester, and early expression being concentrated in astrocytes of the cortex, this can be interpreted to mean that aromatase plays a critical role in the sexual differentiation of the brain[167]. As the brain matures aromatase is observed to be present in the hypothalamus, amygdala cerebral cortex, hippocampus, and cerebellum – the same areas where estrogen receptors (ERs) are found[14].

Positive correlation between aromatase expression and ER distribution has been reported in the human brain[14]. With estrogen down-regulating its own receptors[35, 150] on a transcriptional level[59], this may indicate that overexpression of estrogen may result in the down-regulation of aromatase as well. This interaction was observed in tilapia where E_2 overexposure prior to 10 days of age resulted in the down-regulation of both aromatase and ER-α mRNA expression. It should be noted that developmental interactions between E_2 and aromatase are not necessarily indicative of how they interact in a mature organism.

2.4.1. Interactions with androgens. Only androgens that can be converted to estrogen by aromatase are capable of exerting developmental influence[59]. Fetal testosterone surges, once converted to estrogen, serve to differentiate the male brain by causing ER down-regulation. Gonadectomized male rats showed ER expression comparable to females[59]. Elevated MCH levels leading to inhibition of ACTH may impede sexual differentiation by preventing early

testosterone surges. Additionally, elevated glucocorticoid levels suppress testosterone in the hypothalamus, pituitary, and testes[273]. Steroidal interactions of MCH and glucocorticoids may interrupt typical sexual differentiation of the brain.

2.4.2. Cyclooxygenase-2. Cyclooxygenase-2 enzyme (COX-2) increases prostaglandin E_2 (PGE_2) production, which upregulates aromatase and subsequently E_2[70]. COX-2 expression has been shown to be upregulated by IL-1β and TNF-α in rat brains[138] and in human uterine tissue[70]. With E_2 capable of driving up MCH levels, and MCH levels exerting transcriptional control over IL-1β and TNF-α, it may be the case that a positive feedback loop could drive sustained elevation of E_2. This positive feedback loop has been observed in the human uterus driving endometriosis[70]. Observation of IL-1β and IL-6 inducing COX-2 in the cortical endothelial cells of the rat has been reported[38]. Given the brain locations where aromatase is observed, it is difficult to rule out the possibility that this positive feedback loop might affect human neurological systems as well.

2.5. Estrogen Dysregulation

Aside from more obvious implications in reproduction, estrogen is an incredibly active transmitter throughout the whole body. For the purpose of the theory being presented, the focus will be mostly limited to interactions in the CNS. Key to this endocrine theory of ASD is the manner in which MCH and estrogen appear to have a symbiotic relationship in maintaining homeostasis, which could explain the propensity of a female to experience far less negative impacts from either hormone.

2.5.1. Neurological dysregulation. E_2 has been shown to increase ACTH and corticosterone[33]. With MCH acting to inhibit ACTH secretion this exemplifies one way in which these two hormones work to balance each other. The manner by which estrogen exerts anorectic

influence and MCH exerts orexigenic influence over the hypothalamus[174] has been discussed above. With females naturally having higher basal levels of both hormones, there appears to be a mechanism by which the typical biophysical makeup of a female shows more tolerance to greater fluctuations of estrogen and MCH before pathological symptoms arise. While estrogen and MCH may balance each other behaviorally when it comes to stress and feeding, there are areas where the two synergize. The proliferation of inflammatory cytokines is regulated by estrogen[33] as well as MCH.

HPA response appears to be sexually dimorphic. Adult human males given estradiol patches showed hyper-responsiveness to psychosocial stress compared to controls with inference to impaired glucocorticoid negative feedback mechanisms[127]. Decreased HPA feedback inhibition from glucocorticoids has been observed in rat models as well[96, 279]. It has been reported that the manner by which estrogens affect the HPA axis is missing from the literature[97]. However, these authors describe changes in intracellular calcium ion concentrations which leaves room for MCH being interpreted as the peptide that bridges the gap in this process.

2.5.1.1. ***Dysregulated sexual differentiation.*** Estrogen is solely responsible for the sexual differentiation of the brain[137] as testosterone is converted into estrogen in the brain by aromatase[59]. Areas where sexual differentiation may be the greatest are the hypothalamus, preoptic area, and amygdala as these are areas most sensitive to ER down-regulation as a result of prolonged estrogen exposure[35]. ER down-regulation occurs to prevent excess estrogenic actions especially when estrogen levels exceed normal physiological ranges[150]. The net effect is a “masculinization” of the brain as ER down-regulation reduces the cognitive and emotional influence of estrogen.

ERs play a key role in early brain development. ER-α was strongly represented in the cortex from nine to twelve weeks gestation, decreasing in density by 17 weeks, and ER-β was strongly represented in cortical regions at 17 weeks, decreasing from 20-40 weeks[85]. ER-β has been identified for its role in neuronal migration in the cortex[68, 85] as well as differentiation and maturation of neurons particularly in the hippocampus[68], cortex[68, 85], and thalamus[68]. ER-α is thought to play an important role in early brain development with ER-β playing an important role in later brain development[85].

2.5.1.2. *Dysregulated inhibition and excitation.* Excitation and inhibition are other areas where estrogen and MCH, respectively, balance each other under normal circumstances. Estrogen increases NMDA receptor sensitivity[236], increasing excitatory tone, while MCH generally elicits inhibitory tone. E_2 decreases inhibitory signaling by decreasing GABA synthesis[236, 260]. However, models of excitotoxic brain injury have shown estrogen to be capable of suppressing NMDA receptor input, where GABA production and availability are dependent on estrogen expression as a means to prevent excitotoxicity and seizures[236]. With potential to interact with both glutamate and GABA signaling, dysregulation of estrogen may further contribute to pathological patterns of sensory gating and neurogenesis.

2.5.2. DNA methylation. DNA methylation is one means by which gene expression can be epigenetically altered whereby methyl groups interact with DNA to alter its influence without changing nucleotide sequence. The process of methylation may be indication of environmental influence over genetic expression. The environmental demands for host adaptation lead to changes in gene expression which may influence protein synthesis.

As previously discussed, estrogen levels, MCH levels, and BMI are all positively correlated. While the exact mechanism for this correlation is unknown, methylation has been

implicated. Increasing BMI has been shown to be associated with the decreased methylation of MCHR1 in humans, resulting in higher rates of expression of MCHR1[239]. One plausible explanation may be observed in human patients with obesity, where excess insulin triggers testosterone release from the ovaries, and aromatase in adipose tissue converts these androgens into estrogen[93]. This estrogenic interaction in adipose may influence MCHR1 methylation due to MCH's role in metabolic function, as well as MCHR1 expression in adipocytes.

Estrogen exerts some of its most potent influence on DNA methylation in the CNS. Sexual differentiation of brain regions is the result of sexually dimorphic DNA methylation patterns due to estrogen influencing methylation of ER promoter genes during hormonal surges in mammalian natal development[137]. The early developmental down-regulation of ERs is fixed by increased methylation of promoter genes, resulting in sexual dimorphism of the human brain persisting into adulthood. Estrogen methylation has been discovered in other organ systems as well. Estrogen decreased methylation of CRH receptor 2 (CRHR2) in myocardium, increasing expression and activity of CRHR2 in cultured rat cardiac tissue[51]. Increased CRH receptor expression and activity would lead to increased HPA axis activation and, distally, increased release of glucocorticoids and MCH mRNA.

2.5.3. Environmental endocrine disruptors. There are thousands of new chemicals introduced into the environment each year without a full understanding of how they may be affecting humans. For every compound acknowledged to be harmful there are dozens that have yet to be investigated. These compounds are incredibly pervasive and can be found in food additives and dietary supplements, pesticides, pharmaceuticals, plasticizers, and general pollutants. These chemical have reported effects on cell

growth/proliferation/differentiation/development and inflammation/immune response after binding to ERs[49].

Due to their interactions with neuromelanin and potential to depigment brain regions with visibly dense expression of melanin, heavy metals will be examined first. There are several metals that are categorized as metalloestrogens due to their capacity to exert estrogenic influences. This category includes: aluminum[267], antimony[267], arsenite[267], barium[267], cadmium[128, 267], calcium[128], chromium[128, 267], cobalt[128, 267], copper[128, 267], lead[128, 267], mercury[128, 267], nickel[128, 267], selenite[267], tin[128, 267], and vanadate[128, 267]. Aluminum and cadmium have been described as the most potently estrogenic metals examined so far[128]. Humans come into contact with many of these metals on a daily basis.

One of the most common sources of endocrine disruptors investigated was cosmetic products. 144 women who had elective cesarean sections allowed their fat tissue and milk to be collected to assess for mineral oil paraffins which are widely used in food processing and cosmetics. Observed levels support the contention of bioaccumulation in human adipose tissue and transmission through milk[49]. Another 142 pregnant women – who reported frequent use of various creams and other products such as lipstick – allowed for milk samples and fat samples to be taken during elective cesarean section. Mineral oil saturated hydrocarbon concentration was positively correlated with age, suggesting prolonged use of cosmetics increases the presence of these substances in human fat tissue[50]. With estrogenic compounds being stored long-term in fat tissue, the implications are potentially dire. Adipocytes react to estrogen, and the findings of this review suggest the severity of dysregulation would increase with age. The ability to transmit these estrogenic mineral oil compounds through breastmilk bids great harm to neonates whose developing brain is highly –and permanently – influenced by the presence of estrogen.

Crude and refined petroleum products affect ER-α[265] and ER-β[264, 265] and may disrupt sexual development and dimorphism[264] with relatively low concentrations needed to trigger ER activation in human tissues[265]. With many industrial compounds derived from petroleum, the estrogenic impact is pervasive. Strong evidence exists for a link between environmental pollutants and tissue inflammation[55]. It is through promulgation of inflammation that endocrine disrupting compounds exert their most deleterious effects. Early developmental exposure to bisphenol-A (BPA) - one of the most widely used petroleum-derived chemicals has been shown to exert a significant, dose-dependent effect on the number of neurons and glia in layers V/VI of the cortex[215]. A similar, but non-significant, pattern was observed in layers II/III of the cortex[215]. The changes in quantity of neurons and glia observed in the prefrontal cortex of male rats were not observed in female rats[215]. Pre- and postnatal exposure to polybrominated diphenyl ethers (PBDEs) and PCBs caused dose-dependent alterations in sexually dimorphic brain regions in rats, with lower doses needed to affect males than females[67]. This may provide further support for the female protective factor hypothesis, whereby females can tolerate higher levels of endocrine disruption than males before pathological symptoms present.

Even vitamins can produce estrogenic effects[128]. With prenatal vitamins being recommended to women and vitamin enrichment of a vast majority of processed foods, it can become all too easy to get into ranges of exposure to vitamins that may impact estrogen levels. Obese post-menopausal women experienced increases in serum E_2 in response to supplementation with vitamins C, B_6, B_{12} and folic acid[185]. Folic acid[102, 103] and B_{12}[129] increase tissue response to estrogens. With the tolerable upper intake level of vitamins and minerals for infants being far less than what it is for adults due to differences in body weight, prenatal overexposure to vitamins and minerals may readily enhance or produce estrogenic effects.

2.6. Disorders Comorbidly Diagnosed with ASD

MCH is capable of modulating organ systems beyond the CNS. Considerable overlap with almost all of the comorbid medical and psychiatric disorders seen in patients with ASD and MCH dysregulation is present in the literature. With the HPA axis mediating environmental inputs, inflammation and autoimmune responses, and signaling proteins with receptors throughout the brain and body, these connections will be made clear.

2.6.1. Depression. Depression may be the most significantly related condition to MCH dysregulation[100] and ASD[81]. Mice with higher MCH in the brain exhibited more depressive-like behaviors[75]. MCHR1 blockade in several animal species reduced symptoms of depression[32]. Female mice with MCH signaling genetically ablated showed suppressed depressive behavior[244]. In humans, women who were depressed while pregnant subsequently gave birth to children with increased inflammation persisting into early adulthood[190]. A hyperactive HPA axis, along with increased inflammation, are two of the most consistent biological correlates to depression[190]. Maternal depression has been linked to increased ASD risk[156].

2.6.2. Anxiety. Anxiety may be the psychiatric condition most closely related to ASD[81] and MCH dysregulation. MCHR1 regulates fear and anxiety[196]. MCH has been shown to be anxiogenic[86, 100, 104]. MCHR1 blockade led to reduced symptoms of anxiety in rats[227] and several other species of anima[32]. A state of threat detection and hyper-arousal often seen in anxiety is thought to be the driving force behind difficulty in shifting attention in ASD by over-attending to aversive stimuli in the environment[88]. This anxiety driven hypervigilance is also observed in individuals with enriched CRH gene expression[226, 232] giving further contextual relevance to BI and ASD.

2.6.3. ADHD and OCD. ASD, ADHD, and OCD all show considerable overlap as well[81]. MRI-indicated connectivity within the cortex and interhemispheric connectivity was reduced in patients with ASD, ADHD, and OCD[8]. This pattern of reduced cortical connectivity is in line with pathological expression of developmentally dysregulated GABAergic inhibition which may be induced by MCH. It was noted in that MRIs from patients with ASD and ADHD showed no significant difference in connectivity, and differences observed in patients with OCD showed significant differences to both ASD, ADHD, and the control group[8]. The authors indicate this difference may be explained by the early childhood onset of ASD and ADHD, compared to the typical adolescent onset of OCD[8].

2.6.4. Enteric nervous system dysregulation. The enteric nervous system describes the nerves and signaling pathways which make up a significant portion of the tissue in the lower tract of the digestive system. MCH is produced in the gastrointestinal (GI) system as an immune modulator[284] with MCH and MCHR1 expression in the mucosa of patients with inflammatory bowel disease being abnormally high[133, 284]. MCHR1 mRNA showed a five-fold increase in patients with Crohn's disease, and enteric epithelial cells show up-regulated MCHR1 expression under inflammatory conditions[133]. Enteric nervous system and GI tract inflammation have been found at high rates among patients with ASD[142, 263], with cytokines implicated in these disturbances[211] such as IL-6[31]. Several pro-inflammatory cytokines are transcriptionally regulated by MCH, and in patients with inflammatory bowel disease MCH was found to stimulate IL-8 production[133] – which promotes local recruitment of immune cells – while preventing up-regulation of anti-inflammatory cytokine IL-10 preventing resolution of[284]. GI problems were positively correlated with sensory over-responsivity, and it is suggested that sensory over-responsivity may predict chronic GI problems[159].

2.6.5. Epileptiform activity. Mice with MCHR1 genetically ablated show seizure resistance and the proposed mechanism is how MCH positively regulates NMDA receptor expression in the hippocampus[188]. Moreover, patients with poor seizure control have lower GABA levels[194]. Inflammatory cytokines can trigger seizures[144] via glutamatergic mechanisms and this has been associated with ASD[249]. Approximately 40% of patients with ASD may have epilepsy[106, 263] with females having higher rates of epilepsy than males[1]. Additionally, childhood epilepsy is a risk for future ASD diagnosis with significantly higher rates of ASD in females with epilepsy than males[241]. Epilepsy was also positively correlated with autism symptoms and maladaptive behaviors[1]. Aside from estrogen increasing input sensitivity of NMDA receptors, estrogenic control of epilepsy is observable in patients with catamenial epilepsy, where peaks in circulating estrogen trigger seizures.

2.6.6. Sleep dysregulation. Dysregulation of GABA and 5-HT are suggested to play a role in sleep disorders in children with ASD[263]. Aside from modulating both of those neurotransmitters, MCH neurons have been reported to play a modulatory role on the rapid eye movement stage (REM) of sleep[111]. Ablation of MCH neurons in the hypothalamus leads to disrupted/fragmented slow wave sleep patterns[257]. Females are more prone to insomnia caused by HPA axis dysregulation from stress[33].

2.6.7. Alexithymia. While not an official mental health diagnosis, alexithymia is a term used to describe a condition marked by the following deficits: describing and identifying subjective feelings, engaging in fantasy, distinguishing between emotions and body sensations caused by stress, and theory of mind[71, 246]. Many of the key features of this condition are often assumed to be a part of ASD, but it is helpful to separate the two as not all of the features of alexithymia are consistently observed in individuals with ASD. Alexithymia does have

considerable co-occurrence with GI disorders, eating disorders, and anxiety disorders, particularly panic disorder[246] and subjects with alexithymia report higher body checking behaviors and body dissatisfaction than controls indicating higher risk of eating disorders[57]. Alexithymia and Asperger's disorder share many characteristics in the realm of speech, language, and social interaction[71]. Much like ASD, males tend to express symptomology at higher rates than females[145]. Impaired emotional processing, as indicated by less ACC activation in response to emotion-evoking stimuli[118] and impaired REM sleep[246] fits in with neurological dysregulation that may be explained by aberrant MCH activity. Other brain areas possibly responsible for regulating expression of alexithymia which overlap with MCH expression are the prefrontal and insular cortices, and the amygdala[23]. While eating disorders may be associated with alexithymia, obesity is positively correlated with symptomology, too[63]. With energy homeostasis so closely tied to alexithymia, dysfunction of the hypothalamus and MCH may likely also play a part in this disorder.

2.6.8. Metabolic dysregulation. Insulin and MCH engage in significant crosstalk. MCH stimulates insulin secretion[34, 100, 101] and insulin activates MCH neurons[100] and up-regulates MCHR1 expression[64]. MCH down-regulates insulin receptors leading to insulin resistant states[34, 101] and pancreatic dysfunction[101]. Gestational diabetes was linked to increased ASD risk, especially if obesity was present in tandem[52, 147, 155]. ASD-specific maternal autoantibodies have been found to be expressed at higher rates among mothers who have obesity, diabetes, or hypertensive disorders[134]. Meta-analysis confirms obesity in mothers poses significant risk for ASD in offspring[148]. With genetic models of obesity displaying MCH over-activity[101], and BMI being positively correlated to MCHR1 demethylation, there is much support for MCH having a role in ASD pathogenesis.

While obesity in mothers may play a significant role in their children being diagnosed with ASD, an opposite trend is observed in women with ASD. There is much in the literature to support the idea that anorexia is one way in which ASD may express itself in females[177] where body image becomes the restricted and repetitive preoccupation. A biochemical disturbance has been observed in the urine of males with ASD and females with anorexia nervosa (AN) that is not observed in typically developing children[79]. Feeding problems are overrepresented in children with developmental delays[119], and the co-occurrence of ASD and AN in families suggests a common origin[80, 131, 179]. AN has strong overlap with childhood onset neuropsychiatric disorders with a significant portion having ASD[269]. Females with AN display elevated ASD traits[20, 158, 179, 242, 248, 285]. Social and cognitive inflexibility[158, 248, 285], aloofness[285], and detail focus[179] are traits seen in both ASD and AN. Even after eating disorder symptoms were in recovery, high rates of ASD, OCD, and obsessive compulsive personality disorder were observed in women who had received treatment six years prior for teenage onset AN[200]. Alexithymia was found to be associated with AN[247] and severity of alexithymia was positively correlated with a worse prognosis in the course of recovery[237].

In anorexia-cachexia syndrome it is proposed IL-1, IL-6, and TNF-α act on the hypothalamus leading to increased CRH expression with CRH receptor activation having potent anorectic effects[199]. IL-1β acting on the hypothalamus and cytokine positive feedback loops have also been implicated in anorexia-cachexia syndrome[198]. Ovariectomized rats given E_2 at normal physiological ranges countered the orexigenic effects of MCH[50]. With estrogens and MCH in careful balance, the pubertal surge of estrogen may push females into the realm of pathology and explain the suggested common environmental interaction that causes ASD in infant boys and AN in girls at puberty[80]. Males having a lower threshold for environmental

endocrine disruption than females has been discussed and is in line with the observation that ASD expression in females is often delayed until puberty.

3. Discussion

A wealth of information about ASD and the systems underlying the disorder has been published over the years, and this research activity continues to increase in volume. However, attempts to synthesize this information into a uniform theory have apparently eluded the scientific community. This paper has attempted to explain the expression of ASD by investigating a previously unexamined biological system – the MCH system – and its role in the larger context of endocrine functions. With origins in the neural crest, and the functions of this embryonic formation's other derivatives, it is easy to understand how melanin and its governing hormones play a significant role in the host surviving and managing environmental insult. Human beings possess varying degrees of visible melanins. Given the protective role of melanin – and the resilience of eumelanin – observation of anecdotal evidence seems to suggest that populations with higher eumelanin expression show fewer visible signs of oxidative stress that normally accompanies the process of aging.

The biological process of α-MSH blocking pro-inflammatory and autoimmune cytokines discussed above provides support for anti-inflammatory protection of the host, but α-MSH's influence may not to be the same extent as the mediators of inflammation. It is necessary to consider that variations in pigment expression and the hormones responsible for creating melanin – with importance given to which type – may explain subtle variations in susceptibility to a positive feedback loop, which has potential lifelong effects on the central nervous system and behaviors regulating how an organism perceives reality and interprets events into meaningful experiences which influence subsequent interactions.

Pigmentation expression can vary in eyes, hair, and skin – in order of how much these patterns of melanin expression may measurably influence behavior, temperament, and cognition. While there may be a lack of literature with which strong inference may be conferred as to a relationship between visible melanin and internal melanin expression, a wealth of medical information does suggest that there are racial differences in the prognosis and susceptibility of disease.

3.1. ASD as a Complex Reaction to Endocrine Dysregulation

The information presented above highlights a manner by which endocrine dysregulation may propagate widespread inflammation, signaling protein dysregulation, and genetic changes in the epigenome and transcriptome. The intent of this paper was to afford an overview of the maximum biopsychosocial dysregulation possible at each step in the proposed endocrine system positive feedback loop. It is outside the scope of this paper to assess how varying rates of exposure to– not to mention varying potency of – environmental endocrine disruptors may alter the systemic function of the human animal. What will be discussed are the implications this model carries when considering the origin and treatment of metabolic and mental illnesses. Specifically, severe endocrine dysregulation may trigger the developmental events responsible for producing the myriad of disorders grouped together under the classification of ASDs as a result of the common origins and pervasive entanglement of the CNS, immune, and pigmentation systems.

3.2.1. Genetics in ASD formation. The empirical data to suggest a Mendelian genetic link to ASD is incredibly weak. This theory presents ‘high confidence’ genes that are capable of explaining for – at best – four percent of the ASD cases known, and assumes a theory of ‘multiple genetic hits’ to compensate for this weakness in correlation. This is further

confounded by findings that so called 'rare variants' can be found in typically developing individuals[203]. There is no evidence of sexually dimorphic expression of ASD 'risk genes'[270]. Further, refinement of processing whole exome data has lead to acknowledgement of underrepresentation of post-zygotic mosaic mutations – non-germline variations[2]. This has spurred a reexamination of ASD simplex cases resulting in a discovery that post-zygotic mosaic mutations made up a significantly overlooked portion of de novo mutations[135, 149]. This method of identifying when a mutation occurred in the lifespan of an organism is still rather new, but it is difficult to see this trend reversing as the process is improved.

Explanation for non-germline mutations occurring after fertilization strongly suggests teratogenic activity – the embryo needed to make significant sacrifices to enable survival in conditions that might otherwise result in miscarriage. These sacrifices come in the form of altered signaling pathways in the CNS to mitigate the otherwise fatal presence of the proteins acting upon them in utero. LD50 – lethal dose for half the population exposed – is measured in mg toxicant to kg of bodyweight. With a human fetus not reaching a kilogram until the third trimester, the tolerance for environmental insult is exponentially smaller for the developing embryo than a 70kg adult. Adaptation was the only option to survive. Additional consideration for the heritability of ASD should examine how methylation patterns consistent across multiple generations result in DNA changes. This is the very core of epigenetics – the process by which the environment necessitates genetic mutation.

While there may be inconsistent data available for rare variants and their link to ASD there may be chromosomal interactions which offer insight into the formation of this neurodevelopmental disorder. Chromosome 6q has been implicated in ASD[37, 195], particularly 6q16 being associated with glutamate receptor dysregulation[110]. Chromosomal localization of

MCHR2 has identified chromosome 6 along the region 6q16.2-16.3[209]. The modulation of glutamate has been framed as a function of MCH and further supports its developmental role in ASD.

3.2.2. Developmental neurological dysregulation in ASD formation. Disruption of the migration and formation of pyramid neurons and interneurons in the cerebral cortex has been proposed to be a key cause for the observed differences in neural density and connectivity issues along with the excitatory-inhibitory dysregulation in the cortex of individuals with ASD[40]. Dysregulated cortical connectivity in area S1 was associated with tactical processing abnormalities while dysregulated connectivity from area S1 to S2 was correlated with an increase in abnormal multisensory processing in ASD[122]. Minicolumns in ASD brains are in higher quantity, but smaller in size[41]. The increased number of minicolumns in the ASD brain suggests a gestational disruption of layer V pyramidal cells and clusters of layer II/III cells[42]. ASD brains show increased spine densities in layers II[107] and V[107, 245] inferring an excess of excitatory inputs, impaired sensory gating, alongside impaired long range cortico-cortical and cortical-subcortical communications[245]. Human infants who were later diagnosed with ASD at 24 months showed connectivity deficits in key cortical areas in brain scans at six and 12 months[146].Of particular interest related to the excitation and inhibition dysregulation of the cortex is the role this problematic situation plays within the context of sensory gating. Dysfunction of the NMDA receptors at excitatory synapses has been found to be associated with ASD[141]. This interruption of glutamate signaling at NMDA receptors leads to diminished excitatory tone. In studies illustrating mouse models of NMDA receptor hypofunction, deficits in social and communicative functioning, in combination with increased self-injurious and repetitive behaviors, were reported[72]. Carlsson proposed that ASD was a hypoglutaminergic

disorder, noting the similarities between ASD and pharmaceutical blockade of NMDA receptors – stimulus overselectivity attributed to abnormal sensory gating alongside difficulties in grasping wholeness and context[39]. Adults with ASD were shown to have sensory gating impairments as evidenced by prepulse inhibition of startle response[160]. Sensory gating problems – as measured by cortical P3 event-related potential – suggest individuals with ASD experience dissociation to speech sounds[30] in conjunction with language performance and stimulus discrimination errors[56]. The loss of precision in sensory integration due to disrupted inhibitory and excitatory tone of the cortex resultant from dysregulated MCH may explain the frequent speech processing deficits in individuals with ASD[17]. This disruption of the coordination and interpretation of sensory inputs from the environment may facilitate the contextually inappropriate displays of obsessive-compulsive thoughts and behaviors observed in ASD[181, 193, 240]. Also, impaired multidirectional flow of information in the cortex of individuals with ASD has been proposed to contribute to deficits in attending to the environment in flexible, productive and meaningful ways[254]. Functional magnetic resonance imaging (fMRI) has shown that executive function deficits in ASD are associated with reduced functional connectivity of the frontal cortex with other cortical and sub-cortical regions[89]. Compared to typically developing peers, males and females with ASD showed hypoconnectivity in the default mode network[278]. The medial prefrontal cortex and lateral temporal cortices have been identified as brain regions responsible for governing navigation, theory of mind, autobiographical memory, and default resting mode[238].

Autobiographical memory pertains to the assimilation of self in the context of events previously experienced. Males with ASD are reported to have trouble recalling autobiographical memories[105]. In male and female children with ASD autobiographical memory was impaired in comparison to typically developing peers matched for age, gender, and IQ with less reference to

emotion and less specificity in remote memories, and less ability to recall semantic and episodic memories when cued by lifetime periods[83]. However, verbal memory was preserved in the group with ASD[83]. This study also showed associations between executive function impairments and autobiographical memory deficits. Impaired access to prior events and experiences may lend itself to poor predictive skills, which has been suggested to be a contributing factor in the manifestation of the self-stimulatory behaviors common in ASD[191, 230].

Of key interest to this endocrine theory of ASD pathogenesis is the anterior cingulate cortex (ACC). This cortical sub-region receives direct projections from the hypothalamus and is thought to be responsible for mother-infant interactions, cognition, motor control, conditioned emotional learning, assessment of motivational interactions, verbal communication of internal states, and assignment of emotional valences to internal and external stimuli[23]. Reduced glutamine signaling in the ACC was shown in adults with ASD[249] which may be further explained by aberrant MCH influence. Additionally, innervations of dopamine, 5-HT, and noradrenaline are assumed to be responsible for the emotional functions of the ACC. Interpretation of data investigating this emotional locus of control has concluded that alexithymia may be the result of ACC dysfunction[23]. The ACC also sends and receives projections to/from the LC with the dialog between these two brain sites determining level of arousal based on environmental context[84]. Persons with ASD showed weaker P3 activity in response to both social and non-social reward opportunities implicating weak selective and focused processing (phasic) modes of the LC[132]. In the discussion of neurological disorders, patients with Alzheimer's and Parkinson's disease have reduced quantities of LC neurons[13], and Alzheimer's patients with the greatest cognitive impairment present the most elevated levels of MCH in their cerebrospinal fluid[225].

There are fiber clusters in postmortem ASD brains which are more robust than TD brains. These clusters connect to cortical/subcortical regions. Fiber tracts identified are related to the corpus callosum, cerebellum, and areas of the cortex that are responsible for speech and fine motor control communication with the frontal lobe. White matter in the ventral diencephalon was shown to be more robust in postmortem ASD brains compared to controls. Enlarged thalamus, hypothalamus, and zona incerta were noted. The zona incerta is responsible for the majority of MCH production and has projections to much of the cortex[281].

Aberrant MCH expression and signaling during gestational and developmental months of a developing child offers insight as to how ASD manifests. During the formation of the cortal layers of the brain, too much MCH inhibits GABA and glutamate signaling leading to delayed – possibly halted – neurogenesis of layers II/III/V of the cortex along with poor interconnectivity across cortical regions due to disrupted minicolumns formation. This alteration of the hardware leads to impeded ability to acquire the software – various behavior chains necessary to take information in, map meaning to reality (creation of perception), and respond to novel situations adaptively by drawing on the stored perceptions of reality. Impaired sensory gating, resulting from dysregulation of GABA and glutamate, aids in the development of restrictive and repetitive thinking and externalization of behavior chains. NSSI may be used to lower MCH levels since physical pain drives this, likely due to β-endorphin cleaving from POMC necessitating a brief upregulation of POMC and its derivatives – ACTH, α-MSH, and β-endorphin among others. Upregulation of ACTH, independently of CRH release, working in tandem with upregulated α-MSH would serve to arrest inflammation. This process may explain why exercise is such a potent contributor to the downregulation of MCH and resulting inflammation; β-endorphin production from exercise upregulates POMC signaling and transcription.

3.2.3. Estrogen dysregulation in ASD formation. Altered differentiation in brain areas where sexual dimorphism is typically greatest has been associated with ASD risk[163]. In support of this association is the enhancement of brain functions that are both male and female typical functions in individuals with ASD[18]. Given that females naturally express more estrogen and MCH, there is a possibility that female protective factors may result in a greater tolerance for fluctuations in levels of both in order to cope with the biological demands of hormone fluctuations experienced throughout the menstrual cycle. With estrogen having significant potential to alter brain organization and function, being biologically female may bear additional buffering against the severity of ASD symptoms. Brain activity measures indicate that in early childhood, girls with ASD showed patterns of brain activity that matched a typical boy of the same age[242]. Hypothetically, overexposure to estrogen during gestation leading to decreased expression of ERs and aromatase, a typical female brain would undergo differentiation patterns that resemble typical male development while males may experience pathology due to even further loss of ER activity which is needed to support proper cognitive function. In postmortem brains from individuals with ASD, both ER-β and aromatase mRNA were reduced[53]. Without effective conversion to estrogen, elevated testosterone levels could mistakenly be viewed as the cause of ASD rather than a symptom. This concept is supported by findings that fetal testosterone levels had no correlation with ASD traits[136]. Further disproof of fetal testosterone causing ASD is the lack of accompanying physical traits dependent on testosterone[18].

The process of CRHR2 expression being regulated by estrogen driven gene methylation may explain why women with ASD are reported as having higher frequencies of cardiac conditions[197]. Women generally have higher basal HPA axis activation than males which may explain why women reach levels of CRH which impact the heart before males do. CRH

signaling takes place during HPA axis activation and stress which may provide a reasonable link to ASD. These authors infer that abnormalities in calcium ion channels are a common thread in neurological and cardiac conditions in ASD[197]. Genes relating to the methylation and regulation of synaptic vesicle release through calcium ion channels have been implicated in autism[60] as well. Additionally, exogenous estrogen disrupting compounds have been suggested to be an epigenetic cause of neurological dysregulation of ASD, also explaining for differing rates of expression between males and females[126].

In an exploration of these endocrine disrupting compounds, it was found that polychlorinated biphenyl (PCB) 95 altered methylation of genes that regulate neuronal synapses, transcription, and transduction pathways, and the investigators report significant overlap of gene expression altered by PCB 95 with rare variants expressed in ASD[61]. PCB exposure in utero was associated with higher rates of ASD[154]. The proposed routes in this study were endocrine and immune disruption affecting neuronal development and mediating epigenetic effects. Examination of the methylation patterns in autism has been interpreted to mean epigenetic transcriptional suppression could be the origin of ASD[65]. Heavy metals are both estrogenic and melanin reducing in human tissues. Hypopigmented humans are the global minority – and also the most susceptible to environmental insult due to enriched expression of pheomelanin – it may be possible that heavy metals more significantly contribute to ASD in humans who align with type I or II on the Fitzpatrick phototyping scale. It known is from studies of postmortem brains donated by individuals with ASD show significantly higher concentrations of aluminum, particularly around astrocytes, glial, and microglial cells[166]. Aluminum exerting estrogenic effects on astrocytes, glial and microglial cells may produce conditions of enhanced pro-inflammatory cytokines commonly seen in ASD[262]. Autoimmune and pro-inflammatory

signaling are suggested to be the cause of microglial activation[171, 172] and abnormal microglial-neuronal spacing in the dorsolateral prefrontal cortex seen in patients with ASD[171]. Genetic markers for enriched astrocyte and activated microglial cell expression in ASD were associated with changes in the transcriptome attributed to environmental factors[262]. While aluminum is a potent estrogenic element, it is not the only exogenous source of estrogen capable of driving these pathologies. Aluminum is transmittable in breastmilk and has the capability to alter gene expression[267]. Thus, aluminum appears to pose a significant risk in the development of ASD.

Since many of these endocrine disrupting compounds are capable of being transmittable in breastmilk and stored in fat cells, this could explain why maternal half-siblings with ASD pose a significant recurrence risk, but not paternal half-siblings[90]. The gestational presence of elevated endocrine antagonists leads to altered genetic expression. When cortical DNA methylation profiles were examined in post-mortem brains from donors with ASD, correlation was found among ASD, synaptic transmission, GABA metabolism and signaling, and chemokine production – such as TNF[175]. Alteration of these systems parallels the dysregulation anticipated in the wake of dysregulated MCH expression and signaling.

3.2.4. Immune dysregulation in the formation of ASD. Immune responses in the context of the endocrine theory of ASD pathogenesis will fall under the categories of pro-inflammatory or anti-inflammatory. Brain and CNS inflammation, in tandem with increased cytokine production, has been observed in postmortem brain tissue of both old and young persons with ASD[78]. For this reason, this paper will focus more on the discussion of inflammatory immune responses.

Females show greater susceptibility to stress-induced autoimmune and inflammatory diseases, with estrogen decreasing glucocorticoid sensitivity and increasing cytokine

production[33]. Pro-inflammatory cytokines disrupting the hypothalamic regulation of lutenizing hormone and ovulation may explain why infertility –particularly in mothers who have used fertility treatments – has been proposed to be a risk factor for ASD in offspring[155]. Maternal immune activation has been associated with autism[66] with the following cytokines bearing significance in the pathogenesis of ASD: IFN-γ[180], TNF-α[66], ILs 1β, 6, 12[66, 180,], along with ILs 2, 4, 5, and 8[6]. A gestational, day one increase in IL-6 may be the trigger for gestational cytokine imbalance responsible for subsequent developmental disruption[192]. Due to the ability of immune responses to change receptor expression, aberrant immune activity during critical periods of neurodevelopment may participate in the neurological dysfunction associated with ASD[11], with key targets being the cerebral cortex[66, 152, 277] and hypothalamus[66] where maternal antibodies bind[78]. IL-17A has been shown to be the most significantly correlated cytokine to ASD-like phenotypes[45, 123, 192, 277] due to neurodevelopmental dysregulation[123, 277]. With the potential to elicit enduring activation of MCH receptors, the cortical irregularities associated with IL-17A may be due to the suppression of GABA during key periods of development, preventing typical neurogenesis. Given aromatase concentration in early development is predominately found in astrocytes of the cortex, and astrocytes being capable of producing IL-17, the pathway between endocrine dysregulation and immune enhancement becomes more evident.

While it is true typical females have higher autoimmune and inflammatory immune dysregulation compared to typical males, sex-specific gene expression in males with ASD revealed higher expression of autoimmune and inflammation genes[270]. Maternal immune activation may prime the transcriptome of males who are later diagnosed with ASD. Cytokine up-regulation feedback loops have been observed in the human uterine tissues during endometriosis[70], illustrating the potential for the gestational origins of sustained cytokine

imbalances which may result in the pathogenesis of ASD in offspring. Maternal immune activation in humans showed IL-6 overexpression resulting in altered connectivity between the amygdala and brain regions involved in sensory processing and integration, salience detection, learning and memory, and lower impulse control in offspring by two years of age[87]. Preterm human infants, whose neuro-connectional profiles were observed in fMRIs, indicated diminished functional connectivity were all born of mothers whose placentas all showed signs of inflammation[251]. Because of the ways in which inflammatory cytokines recruit additional cytokine activity, it may be difficult to assess each one in isolation because their synergistic effects are so pervasive.

The role of cytokines in ASD and related disorders was reviewed, resulting in the identification of many cognitive and behavioral associations[180]: a) sustained IL-1β in the hippocampus was associated with impaired spatial memory. IL-1 was found to alter sleep patterns and increase social withdrawal; b) IL-2 expression was associated with increased repetitive behaviors; c) increased plasma levels of IL-6 were associated with depression; d) TNF-α was found to induce neuronal apoptosis and elicit social withdrawal. Additional findings for genetic ablation or blockade of IL-1β, IL-4, and IL-6 being associated with impaired memory and cognitive function[180] may indicate differences between expression of cytokines and their respective receptors. It is usually the case where signaling proteins down-regulate their own receptors in an attempt to attenuate deleterious effects caused by too frequent or prolonged activation of the receptor. This could lead to cytotoxic conditions whereby overactivity of these particular cytokine receptors leads to death of the cells with the receptor – the basis of inflammation's role in neurodegeneration.

Cytokine levels in the plasma of children with ASD resemble myeloid cell activation[180], and with myeloid cells originating in bone marrow[282] it is reasonable to suggest MCH may be involved in this cascade of immune dysfunction. An increased presence of 5-HT, due to cytokine activity, and MCH restraining GABAergic activity, could explain this gestational neurological dysregulation. These immune interactions in the brain are a plausible explanation for why increased 5-HT in peripheral blood platelets has been observed in approximately one-third of patients with ASD[11]. Additionally, IL-17A was found to be elevated in a large portion of children with ASD, with IL-17A levels positively correlated with autism severity[5]. With IL-17 being shown to act on MCH receptors and its correlation to ASD severity, T_h 17 cell differentiation may be a strong indicator of ASD severity as well.

3.2.5. Light and melanin in the formation of ASD. The epidermis has the machinery and materials to synthesize serotonin. Constituents of the epidermis – particularly melanocytes – and much of the brain areas previously mentioned have common embryological origin. This dynamic is responsible for the seasonal expression of psychopathology[216]. With too little absorbable sunlight, the body may engage the immune system –ramping up MCH production – in anticipation of the cooler months and the infections with cyclically increased virulence. MCH release would serve to decrease the light dampening presence of melanin in the skin while also triggering pro-inflammatory cytokines which may provide a temporary boost in 5-HT until enough sunlight penetrates the skin to trigger α-MSH and 5-HT production and release. As α-MSH levels rise, the production of MCH is gradually decreased while anti-inflammatory cytokines begin balancing immune responses. This balancing of the immune response leads to a decrease in the cytokine driven production of 5-HT so as to maintain homeostasis in 5-HT

signaling throughout the year as sunlight intensity –and α-MSH expression and signaling – changes.

One final examination of a correlation between race and ASD must be addressed. Research investigating a birth cohort in Sweden identified that children of Somali immigrants developed ASD at four to five times the rate of the Swedish population, and the mothers were found to have low vitamin D[19]. MCH could be the reason these children of Somali immigrants were born with ASD. α-MSH levels have a seasonal rate of expression positively correlated to available sunlight. MCH levels have a diurnal fluctuation negatively correlated to daily sunlight levels. With low vitamin D levels, the mother's body may have been attempting to adapt to higher latitudes where there is less sunlight by facilitating the ability toabsorb sunlight through her skin in order to produce vitamin D. Depending on how industrialized the areas of Somalia are from which these individuals emigrated, there may also be a difference in environmental endocrine disruptors. Higher MCH levels would suppress eumelanin melanin production as AgRP levels rise in tandem. Skin lightening might gradually take place to allow more sun light into the areas of the dermal tissue where vitamin D synthesis takes place. Elevated MCH levels and suppressed α-MSH levels would lead to a greater presence of inflammatory cytokines that may synergize with the elevated MCH. This synergistic interaction may interfere with developmentally essential excitation and inhibition signaling producing altered neuronal connectivity in the cortex, hypothalamus, and other areas of the brain and body where MCH receptors are found.

3.2.6. Contributing factors to systemic MCH dysregulation and ASD. Another inflammatory concept which needs to be addressed to help clear up misinformation that has persisted over the years: refrigerator mothers cause ASD. This is a double edged sword, because

as it stands mothers who are not very warm and nurturing are not causing ASD in their infants so much as the mother is suffering HPA over-activation herself, and this is passed on. Mice with genetically ablated MCH receptors displayed maternal aggression, poor nesting, deficits in pup retrieval, and impaired milk production[6]. It is suggested that MCH may only be needed to initiate maternal behavior and not to maintain it due to MCH injection into the POA being shown to decrease maternal behavior in rats[202]. In this context, the affect of the mother should be considered a symptom of inflammation and HPA dysregulation in need of support, and in no manner is it the mother's fault her child has ASD.

In the context of ASD in natively western populations – people residing in the United States, United Kingdom, Australia, and Western Europe – the degree of industrialization and cultural differences may play a larger role in ASD rates. Food processing is a necessity to provide foods that are free from spoilage. Food processing and storage has been identified as the means by which mineral oil paraffins enter the food supply and are considered the most significant route for estrogenic endocrine disruptors to enter the human body. Ways in which the food supply has been compromised with estrogenic compounds include, but are not limited to: a) jute fibers used to make the burlap sacks that hold rice, cocoa, nuts, etc. are treated with mineral oils; b) animal feeds enriched with used cooking oils obtained from collection services which did not exercise proper separation from motor oil and other industrial lubricants resulting in tainted meat and eggs; c) plastic food containers and paper food containers treated with waterproof linings[49]. Additionally, an anthropological view may consider the amount of time spent outside in the sun light fifty years ago compared to now with cultural shifts in entertainment leaning more towards consumer electronics – televisions, smart phones, computers, video games, etc.

All of these cultural practices converge on the common theoretical framework posited in this paper: ASD is the culmination of endocrine-mediated inflammation, wherein the primary environmental input is estrogen, the primary bodily output is MCH, and the resultant cytokine expression synergizes with MCH to drive neurological dysregulation affecting social and communicative skills, executive functioning, sensory gating, emotional awareness, theory of mind, memory formation and recall, integrating environmental and subjective stimuli into a meaningful experience, and proprioception. The underlying reason autoimmune activity takes place is to reduce signaling activity by attacking the receptors and neurons, inducing excitotoxic death when expression of the signaling proteins cannot be attenuated (See Figure. 2). Just as there are redundancies of the systems maintaining the endocrine and inflammatory bias in this theory, each individual has their own biological redundancies which are recruited to maintain typical development and function. This, in combination with widely differing exposure to the myriad of environmental toxicants may explain the varied expression of ASD observed in the global population. In addition to the conditions which may initiate this positive feedback loop, the possibility for immune response to initiate the feedback loop exists. However, without suppression of POMC and α-MSH this outcome may be less probable.

3.2. Implications for Treatment and Prevention of ASD

One of the most promising treatments discovered in the literature relates to nonsteroidal anti-inflammatory drugs to blockade the COX-2 enzyme. In a double blind, placebo controlled trial children with ASD who were taking risperidone were given either a placebo or a pharmaceutical COX-2 inhibitor, resulting in significant beneficial decreases in irritability, stereotypy, and social withdrawal[10]. Both COX-2 blockade and genetic ablation attenuate the anorectic responses to inflammatory cytokines without increasing hypoglycemic drive[112]. The

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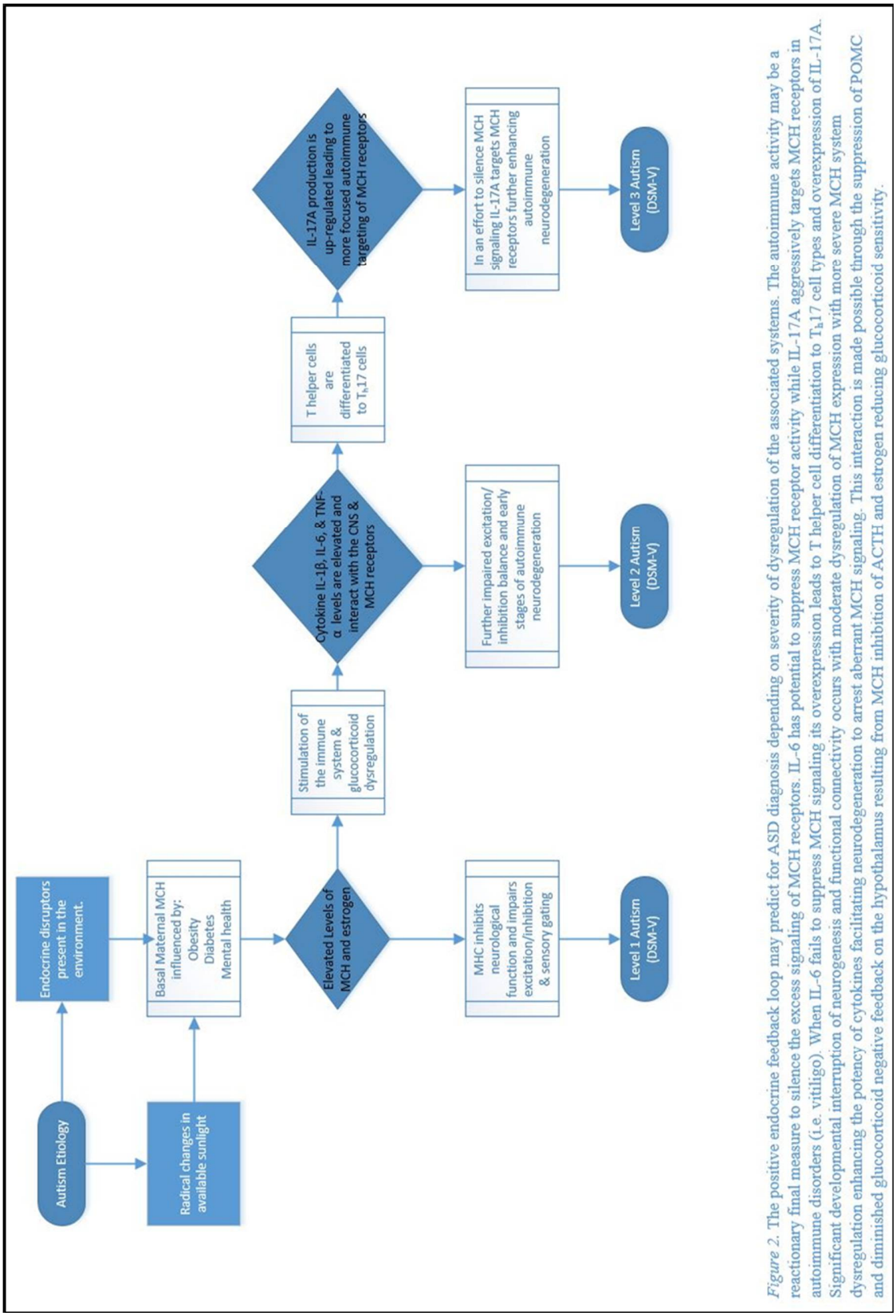

Figure 2. The positive endocrine feedback loop may predict for ASD diagnosis depending on severity of dysregulation of the associated systems. The autoimmune activity may be a reactionary final measure to silence the excess signaling of MCH receptors. IL-6 has potential to suppress MCH receptor activity while IL-17A aggressively targets MCH receptors in autoimmune disorders (i.e. vitiligo). When IL-6 fails to suppress MCH signaling its overexpression leads to T helper cell differentiation to T$_h$17 cell types and overexpression of IL-17A. Significant developmental interruption of neurogenesis and functional connectivity occurs with moderate dysregulation of MCH expression with more severe MCH system dysregulation enhancing the potency of cytokines facilitating neurodegeneration to arrest aberrant MCH signaling. This interaction is made possible through the suppression of POMC and diminished glucocorticoid negative feedback on the hypothalamus resulting from MCH inhibition of ACTH and estrogen reducing glucocorticoid sensitivity.

ability of COX-2 inhibition to improve ASD symptomology, counter response to inflammatory cytokines, and do so while avoiding the unbalancing of other endocrine signaling pathways – like insulin – indicates this may be a potent means to assist in arresting the positive feedback loop driving ASD. With developmentally timed α-MSH doses delivered to rat pups causing increased gregariousness in males, it could also be beneficial to explore primate models of this interaction. If α-MSH serves to improve social interaction in mammals who also express MHCR2 there is a possibility this may be a viable treatment in humans.

Exercise is a potent regulator of MCH expression. Mice who were repeatedly subjected to induced stress showed signs of depression and transcriptionally up-regulated MCH levels that were reversed by forced exercise[124, 125]. Thus, exercise may be another means by which inflammation and MCH may be mitigated, and it is a relatively low-cost intervention with few or no negative side effects. The potential use of exercise to transcriptionally suppress MCH addresses several concurrent ASD risk factors: depression, obesity, insulin resistant metabolic states, and inflammation. Exercise programs are generally inexpensive to implement, especially if calisthenics are the primary form of exercise. This is a biopsychosocial approach because it can support biological needs, and improve deficits in motor skill function and proprioception. Implementing exercise as a group activity also provides opportunities to enhance social-communication and emotional skills.

Diet is another potential MCH-related intervention. A diet lower in fat and sugar content would help with aberrant expression of insulin and reduce inflammation caused by adipocytes. Careful selection of food products – especially buying single ingredients and making food from scratch – could be empirically investigated to determine if such a dietsignificantly reduces the intake of estrogenic endocrine disrupting compounds. Additionally, lignin in dietary fiber can

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bind to free estrogen in the digestive tract and eliminate it from the body, stimulate the production of sex hormone binding globulin which reduces the quantity of biologically active circulating estrogens, and inhibit aromatase, further reducing estrogens in the body[93]. Counterintuitively, avoiding meat whenever possible may help to prevent excess estrogens and MCH because the androgens in meat are aromatasable.

Susceptible populations might consider planning for conception with seasonal fluctuations of available sunlight in mind. Immigrants to countries of greater latitudinal distance from the equator compared to their country of origin may do well to spend 1-2 years allowing their body to adapt to the changes in available sunlight before attempting to conceive. Conception in the first quarter (January-March) was associated with higher rates of ASD and other learning disabilities while conception in the third quarter (July-September) was associated with the lowest rates of these disorders[156]. In all cases, planning for conception in the third quarter (July-September) may also help to mitigate the seasonal rhythm of α-MSH levels, especially if the geographical location is a great distance from the equator.

3.3. Areas of Future Research

Alzheimer's disease is identified with 90% specificity and sensitivity using a panel of 10-20 proteins[280]. Similarly, future research could be conducted to identify signaling proteins and cytokines prenatally or at birth via blood and/or placental tissue examination which serve as definitive biomarkers for ASD diagnosis (see Table 1). Given the shared environment and developmental timing of gestational neurogenesis, it may be possible to identify ASD from a similar blood panel in the mother at 20-30 weeks gestation. The panel could eventually be fine-tuned to help differentiate between the varying expressions of ASD by monitoring specific signaling proteins and cytokines. With a blood panel that could identify ASD in utero, it may be

Table 1

Proteins of interest in ASD pathology

2-arachidonoyl glycerol	arachidonoyl ethanolamide	2-arachidonoyl-glyceryl-ether
O-arachidonoyl-ethanolamine	N-arachidonoyl-dopamine	oleamide
melanin-concentrating hormone	melanocyte-stimulating hormone	corticotropin releasing hormone
adrenocorticotropic hormone	agouti related protein	estrogen
serotonin	N-methyl-D-aspartate	GABA
Glutamate	β-endorphin	cyclooxygenase-2
Interleukins: 1 (family), 2, 3, 4, 5, 6, 8, 10, 12, 17 (family), 22, 23	Cytokines: interferon family, tumor necrosis factor family	Glucocorticoids: corticosterone, cortisol

Table 1. Proposed list of proteins to compare in serum samples of children aged 2-5 with childhood autism and neurotypical age matched peers for the development of a biomarker assay to identify autism.

possible to begin pharmaceutical interventions, for example, utilizing developmentally timed supplements of α-MSH to help reduce inflammation in the mother and child. Development of radioligands specific to receptor types found in the human nervous system could help identify and typify ASD subtypes. At best fMRI can show activity with respect to location in the CNS, but it does not indicate to what extent which signaling proteins are capable of acting in those locations. Knowing if there is excess or absence of specific receptor types, and in which brain regions, may better inform treatment.

With only one known study investigating the effectiveness of COX-2 inhibitors being used to treat people with ASD, further investigation is warranted. Drugs that modulate PGE_2 and aromatase expression are also potentially valuable routes of investigation. Prevention of further estrogenesis in the host may significantly contribute to the attenuation of the endocrine dysregulation positive feedback loop and associated behavioral expression. Interacting with the other side of the loop directly – estrogen, MCH, and cytokines – bears the potential for too great a tradeoff considering how essential they are for normal function of the brain and body.

IL-10 deficiency has been shown to result in inflammatory bowel disease (among other inflammatory responses) due to IL-10's ability to effectively inhibit espression of inflammatory cytokines (IL-1 family, TNF family, IL-6, IL-10, IL-12) and PG production via inhibition of

COX-2 through transcritptional and posttranscriptional means[169]. Delta-9-tetrahydrocannabinol (THC) upregulates IL-10 expression via the stimulation of cannabinoid receptor 2 (CB_2)[283]. The endocannabinoid (eCB) system is regarded as being a key player in the restraint of excess activation of the HPA stress axis through modulation of excitation and inhibition by influencing glutaminergic and GAGAergic signaling[92]. Activation of cannabinoid receptor 1 (CB_1) leads to AVP release independent of both CRH and glucocorticoids resulting in ACTH and POMC upregulation and a net systemic, anti-inflammatory effect[208]. In tandem, CB_1 and CB_2 stimulation attenuate HPA stress axis signaling through increased melanocortin signaling and decreased inflammatory responses both transcriptionally and posttranscriptionally. In addition to AVP, oxytocin secretion is triggered by CB_1 activation[208]. MCH neurons are capable of releasing eCB which serve to later act presynaptically on MCH neurons[91] as another negative feedback loop to help restrain further HPA stress axis activation. The eCB system is further able to influence the excitatory and inhibitory tone of the brain as evidencd by CB_1 receptor expression on 5-HT neurons which inhibit serotonin release[92]. The coexpression of the eCB system with both the MCH system and 5-HT system leads to important research questions: 1) is the endocannibioid system impaired or overactive in individuals with ASD?; 2) with THC inhibiting COX-2 what are the safest preparations of the *cannabis sativa* plant for treatment of individuals with ASD?; 3) Given the implications of pheomelanin in neurodegenerative processes, to what extent has pheomelanin expression impacted United States officials' ability to tolerate change in the law to reschedule cannabis to schedule 2 allowing further research?

4. Conclusion

This paper addressed the lack of interdisciplinary integration of knowledge on the epidemiology of ASD. A biopsychosocial perspective has identified excessive signaling of

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estrogens and MCH producing HPA axis hyperactivation and inflammatory cytokine expression. These cytokines are capable of modulating a positive feedback loop via COX-2 up-regulating PGE_2, resulting in higher transcription of aromatase, followed by increased estrogen expression. Cytokines capable of autoimmune interactions with MCH receptors results in excitotoxic effects – neurodegeneration occurs and developmental neurogenesis are interrupted. The resultant changes in hormones, their receptors, and functional connectivity may later be diagnosed as ASD in children. Investigation of this theoretical framework of ASD may lead to sensitive and specific diagnosis with appropriately developed blood panels.

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