A CRH2-ACTH Theory of Autism Spectrum Disorder

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Abstract. This paper presents a complete theory of autism spectrum disorder (ASD), explaining its etiology, symptoms, and pathology. The core cause of ASD is excessive stress-induced postnatal release of corticotropin-releasing hormone (CRH). CRH competes with urocortins for binding to the CRH2 receptor, impairing their essential function in the utilization of glucose for growth. This results in impaired development of all brain areas depending on CRH2, including areas that are central in social development and eye gaze learning, and low-level sensory areas. Excessive CRH also induces excessive release of adrenal androgens (mainly DHEA), which impairs the long-term plasticity function of gonadal steroids. I show that these two effects can explain all of the known symptoms and properties of ASD. The theory is supported by strong diverse evidence, and points to very early detection biomarkers and preventive pharmaceutical treatments, one of which seems to be very promising.

Keywords. Autism; CRH2; urocortin; ACTH; DHEA;

1 Introduction

Autism spectrum disorder (ASD) is a developmental disorder defined by impaired social communication and restricted, repetitive behaviors [1, 2]. The average global prevalence of ASD is around 1%, higher in high-income countries [1]. Prevalence in 8 year olds in the US in 2020 was reported to be much higher, approximately 4% of boys and 1% of girls [3].

Despite the high public profile of ASD, the extreme burden it puts on patients and caregivers, and extensive research efforts (over 77K/2.2M papers in pubmed/Google Scholar), there is currently no theory of ASD, no early biomarkers, and no preventive treatment. Post-diagnosis treatment is only behavioral (no pharmaceutical treatment), and its efficacy is limited.

Here I present a **CRH theory of ASD (T*ASD)**. T*ASD is the first complete theory of ASD, explaining its etiology, symptoms, pathophysiology, and treatment. The theory is supported by

substantial evidence, and points to novel very early screening and treatment procedures.

Theory overview. According to T*ASD, the core cause of ASD is pre-, peri- or postnatal stress that induces excessive postnatal corticotropin-releasing hormone (CRH) release. The main trigger is a stress-inducing state, but the tendency for excessive stress-induced CRH can be heritable. Excessive release can start prenatally, but the ASD symptoms are mainly due to its postnatal effects. The damage is done during the first year of life, mainly at 3-9 months.

Excessive postnatal CRH impairs normal brain development. This happens via two arms, urocortins and steroids (STRDs). The common aspect of the two arms is prolonged stress-associated signaling at the expense of long-term plasticity signaling.

Urocortins (UCNs) are members of the CRH peptide family, which bind CRH receptor 2 (CRH2). UCNs are released in high glucose states, and are crucial for the utilization of glucose for growth (protein synthesis). In ASD, the excessive CRH yields prolonged binding of CRH2 by CRH instead of UCNs, which impairs the long-term growth effects of CRH2 signaling.

In the second damage arm, excessive CRH induces excessive ACTH, which (in addition to inducing cortisol) is the main inducer of adrenal dehydroepiandrosterone (DHEA), a precursor of testosterone and estrogen. STRDs act via nuclear receptors to support long-term plasticity (differentiation, protein synthesis). However, they also support the initial stages of plasticity via membrane receptors. These two paths are in mutual opposition. DHEA supports rapid signaling, and its excess in ASD impairs the long-term plasticity aspects of gonadal STRDs.

The UCN and STRD arms can explain all of the major ASD symptoms and properties. Impaired social interaction, increased sensory sensitivity (including aversion to touch), impaired eye gaze, and early motor impairment are a consequence of the high CRH2/UCN expression in social, low-level sensory, eye control, and motor brain areas. Impaired social interaction and touch aversion are also explained by the suppression of oxytocin (OXT), an agent essential for social development and pleasant touch, by testosterone and CRH. Repetitive stereotypies and self-injurious behavior such as scratching are directly stimulated by CRH and ACTH.

Limited interests and aversion to novelty are present in ASD because novelty induces CRH release, which people with ASD seek to minimize. These behaviors are a form of self-treatment.

Males are more vulnerable to ASD for at least three partially overlapping reasons. First, estrogen directly supports glucose metabolism and protein synthesis. Second, males need postnatal STRD-mediated plasticity more than females do, as attested by higher release during minipuberty. Third, estrogen stimulates the release of OXT, while testosterone opposes it.

Evidence supporting T*ASD includes direct evidence for increased CRH and ACTH and their effects (e.g., on the sympathetic nervous system and mast cells), and data related to anatomical growth, growth pathways, STRDs, OXT, food intake patterns, comorbidities, and sexual characteristics.

Blood and urine tests for the agents involved in the impaired paths (CRH, ACTH, DHEA etc) during the first postnatal months, and adrenal imaging, can serve for very early identification. There are various possible preventive treatments, probably the most promising being transdermal DHT patches, which reduce CRH and ACTH release.

The paper details the theory, its supporting evidence, and possible treatments.

2 Theory

The core cause of ASD is pre-, peri- or postnatal stress that induces excessive postnatal CRH release. The stress event itself can be minor and/or chronic, with the response enhanced by a tendency for increased release. A large part of the genome supports stress sensing and responses, so such a tendency can involve a large number of small genetic and epigenetic changes. The excessive response can start prenatally, but the ASD symptoms are mainly due to damage done during the first postnatal year (say, 3 to 9 months). The excessive stress responses usually subside after the first year to normal or only slightly increased levels, but their effects persist. Thus, fundamentally, ASD is an 'injury' type disorder.

Excessive postnatal CRH impairs normal brain development via two arms, UCNs and STRDs. The two arms share a common aspect, prolonged stress-associated signaling of an agent at the expense of its long-term plasticity signaling.

2.1 Urocortins (UCNs)

The first damage arm involves **urocortins (UCNs)**, members of the CRH peptide family [4, 5]. CRH acts on two receptors, CRH1 and CRH2, with higher affinity for CRH1. UCN1 binds these two receptors as well, while UCN2 and UCN3 bind only CRH2. The two receptors are G protein-coupled receptors that mainly bind Gs to induce cAMP, but also bind Gi/o and Gq.

The role of CRH1 is to trigger responses to metabolic deficiency (hypo) stress states, including hypoglycemia (hypog), cold, and hypoxia. It triggers the hypothalamus (hthal)-pituitary-adrenal (HPA) stress axis to yield ACTH and cortisol release, stimulates the counter-regulatory responses (CRRs) to hypog via the sympathetic nervous system (SNS), acts in the hthal to increase food intake, and promotes general neural excitability.

Regarding CRH2, at present there is no coherent view of its action, besides a general opposition to some of the effects of CRH1 [4, 5]. T*ASD provides a novel coherent account, distinguishing between CRH2 binding by UCNs (**U-CRH2**) and by CRH (**C-CRH2**).

T*ASD presents a new theory of U-CRH2, whereby its role is to **trigger responses to metabolic excess (hyper) states**, mainly hyperglycemia (**hyperg**), and also heat. In support of this theory, we note that UCNs are released in unstressful situations in response to high meal-induced glucose [6, 7, 8], and that U-CRH2 supports glucose uptake by tissues, insulin release, and glucose utilization for growth (protein synthesis, differentiation) [9, 10, 11, 12, 13, 14, 15, 16, 17, 18]. U-CRH2 opposes CRRs [19], and suppresses appetite and food intake [4].

Due to the low CRH affinity to CRH2, **C-CRH2 is activated in prolonged and/or high stress situations**. While U-CRH2 induces quick CRH2 endocytosis and recycling back to the plasma membrane [20], C-CRH2 delays endocytosis [20], opposes glucose uptake and insulin

signaling [20], and promotes prolonged cAMP production [10]. As a result, **C-CRH2 opposes the growth effects of UCN signaling**.

In ASD, chronic CRH release yields chronic postnatal C-CRH2. This reduces both U-CRH2 binding (because CRH competes with UCNs for CRH2 binding) and U-CRH2 signaling, impairing the learning of all that should be learned during these crucial months. Chronic CRH may also involve chronic activation and desensitization of CRH1.

UCNs are crucial for the development of areas showing CRH2 expression and UCN release. These include the amygdala, BNST, lateral septum, visual cortex, the Edinger-Westphal (EW) nucleus, hypothalamus, auditory cortex, olfactory and touch circuits, motor circuits, and prefrontal cortex (PFC). These areas are those that support low-level sensory inputs (olfaction, vision, audition, touch), sexual and social development, executive function, and regulation of metabolism.

UCNs are also expressed in non-brain tissue, and there are indeed widespread general health problems in ASD [21]. However, the brain is more sensitive to UCN impairment, because in non-brain tissue glucose-induced growth is strongly supported by insulin. In the brain, insulin mainly acts on motor pathways.

2.2 Steroids (STRDs)

The second damage arm in ASD involves **sex steroids (STRDs)**. Excessive CRH induces excessive ACTH, which is known as the inducer of adrenal glucocorticoid (GC, cortisol in humans) release. However, **ACTH is also the main inducer of adrenal dehydroepiandrosterone (DHEA)** [22], the precursor of testosterone and estrogen. At the same time, high CRH reduces GSTRDs via CRH2 [23].

All steroids, including gonadal STRDs and GC, are known to act via nuclear receptors to support long-term plasticity. However, they also support the initial stages of plasticity via membrane receptors that induce rapid intracellular signaling [24]. These two paths oppose each other, because the Ca^{2+}, cAMP and MAPK signaling activated during rapid initial responses interfere with the safe DNA access needed for long-term plasticity. DHEA generally supports rapid signaling, as shown by its direct effects on Ca^{2+} [25] and by its mutual opposition with GC [26, 27, 25]. Thus, DHEA and adrenal steroids (ASTRDs) generally oppose the long-term plasticity aspects of gonadal steroids (GSTRDs).

During the first 1-6 months after birth, human babies undergo **minipuberty**, very high GSTRD release, indicating that GSTRD-mediated plasticity is crucial for early postnatal development. In parallel, the adrenal gland undergoes involution and loses about half of its volume [28, 29]. In ASD, these processes are impaired, and **the excessive postnatal ASTRDs impair GSTRD-mediated development**.

2.3 Explaining ASD symptoms and properties

The UCN and STRD arms of ASD can explain all of the major ASD symptoms and properties, as follows.

Impaired social interaction is a defining characteristic of ASD, explained in two ways. First, there is high CRH2 expression in the areas that support social development, including the BNST, amygdala, lateral septum, and hypothalamus. This indicates that these areas need U-CRH2 signaling, which is impaired.

The second account is related to **oxytocin (OXT)**. The OXT system is one of the most important systems in early postnatal development, when human babies learn that the company of other humans is a positive thing via its association with food and pleasant touch. The role of OXT as an agent essential for the development of sociality is well accepted [30]. UCN3 greatly enhances OXT-induced accessory olfactory bulb plasticity [31]. During the first few years after birth, three is an almost complete overlap between UCN and OXT expression in the hypothalamus PVH and supraoptic nuclei [32]. OXT is directly inhibited by both testosterone [33] and C-CRH2 [34, 35, 36]. These OXT-UCN data further explain the social impairment in ASD.

Repetitive stereotypies (arm flapping, hand twirling, clapping, rocking, head banging) are a defining characteristic of ASD. CRH [37, 38, 39, 40, 41] and ACTH [42, 43] directly induce these types of movements in animal models, including non-human primates, probably because they dramatically increase neural excitability. (See also itch below.)

Limited interests, extreme aversion to novelty, and a desire for order are defining characteristics of ASD. CRH release, which is already basally excessive in ASD, is acutely stimulated by unpredicted inputs [44, 45], and makes male goats show more distress following novelty [46]. Conversely, medial amygdala UCN3 increases preference for novel conspecifics [47]. People with ASD reduce the unpleasant feeling associated with additional CRH release by restricting novel inputs. In addition, brain learning is impaired in ASD, so people with ASD naturally tend to engage in actions and thoughts that they have already learned.

Increased sensory sensitivity is a known property of people with ASD. This happens both because CRH1 promotes sensory hyperexcitability, and because CRH2 is highly expressed in low-level sensory paths. Since early postnatal development mainly involves pruning of excitatory synapses and maturation of inhibition [48, 49], its impairment leads to sustained sensory overload.

Self-injurious behavior is very common in ASD [50] (some stereotypies involve self-injury as well). ACTH, aMSH, and beta-endorphin (other products of the ACTH gene POMC) induce itch and scratching [42, 51], and both ACTH [52, 53] and DHEA stimulate aggression [54, 55].

Aversion to touch is an early sign of ASD. This can be explained by sensory hypersensitivity, ACTH-mediated itch, and reduced OXT, which mediates pleasant touch [56]. The excessive stimulation of the itch path induces an allodynia-like state in which neutral inputs evoke aversive itch signaling.

Impaired eye gaze is a known marker of ASD. The EW nucleus controls learned eye gaze

[57] and contains a population of centrally-projecting neurons with very high UCN1 expression [57]. EW UCN1 is not expressed at birth and gradually increases, showing the importance of UCN signaling to EW development [58].

Early motor impairment is clearly present in ASD [59]. CRH2 is abundantly expressed in skeletal muscle neurons [60], and UCNs act via CRH2 to improve muscle metabolism and growth [61, 62, 63]. STRDs are known to be important for motor development.

Males are more vulnerable to ASD for at least three reasons. First, estrogen, which is higher in females, directly supports brain glucose metabolism and protein synthesis [64]. Thus, the relative female advantage in estrogen covers up for some of the damage done in ASD. Second, minipuberty occurs in both sexes but is much stronger in males [65]. This shows that males need postnatal GSTRD-mediated plasticity more than females do. Relatedly, EW UCN1 expression is 10-1.6 higher in males than in females [66], making male eye gaze learning more sensitive to excessive CRH. Third, estrogen stimulates the release of the social agent OXT [67, 68], while testosterone opposes it [33].

The **spectrum nature** of ASD stems from the wide expression pattern of CRH, UCNs, CRH receptors, and STRD receptors, and the fact that the core cause is stress, which can be highly variable, spatially and temporally. Hence, there is large variability in the ways in which the damage can be manifested.

It is common for babies with ASD to show **excessive passivity** during their first year of life, followed by **hyperactivity** during their second year (and throughout life) [69]. This datum supports high CRH during the 1st year, which activates CRH2 to suppress hunger, cortical norepinephrine, and the SNS. CRH release gradually diminishes, until at some point it can chronically activate CRH1, promoting hypermovement, hunger, food intake, gut issues, etc. Indeed, early life stress has been shown to induce permanent CRH hyperexcitability [70].

Although the public image of **the autistic savant** is clearly unfounded, a small number of papers reported that many people with ASD excel in specific limited areas (e.g., mathematics, visual perception) [71, 72]. In addition, ASD risk is higher with parents with higher IQ and technical capabilities [73]. These data can be explained by a larger number of synapses (especially excitatory ones) due to decreased pruning during postnatal development, and by chronic CRH stimulation of the release of norepinephrine, which promotes memory [74]. Conversely, **intellectual impairment** is highly comorbid with ASD, and is explained by reduced brain (specifically PFC) development.

Cortisol exerts negative feedback on CRH and ACTH secretion. Since STRDs (mainly ASTRDs) oppose GC [75], T*ASD predicts that any situation in which both CRH and ASTRDs (and GSTRDs) are high during development should increase ASD risk. People are especially vulnerable in periods with normally high GSTRDs, because they need their long-term plasticity effects in these periods. This is indeed the case (see PCOS and stress during pregnancy below).

3 Evidence

T*ASD is supported by extensive evidence. The main lines are related to stress, CRH, ACTH, growth (anatomy and pathways), STRDs, OXT, comorbidities, and food intake.

3.1 Stress, CRH, ACTH

There is strong evidence for increased CRH and ACTH, relating to the prenatal, perinatal, and post-damage periods.

Perinatal and prenatal stress. Perinatal stress, which involves high CRH release, increases ASD risk [76]. This includes complications during delivery [76, 77], usage of delivery drugs such as pitocin [77], epidural analgesia [78], neonatal hypog [79], and C-section due to prolonged labor, membrane rupture, or infection (not the C-section itself) [80].

Preterm birth increases ASD risk [1, 81]. This indicates high CRH, because it is a major trigger of preterm birth [82],

Direct CRH and ACTH evidence. Only one paper reported on serum CRH in ASD, and found it higher (4-10yo, n=40) [83]. With respect to ACTH, the following reports showing increased levels were made. Increased serum ACTH and cortisol, with a positive correlation between ACTH and cortisol (6-18yo boys, n=32) [84]. Higher plasma ACTH and beta-endorphin, due to more severely affected ASDs (10$\pm$7yo, n=48) [85]. Higher ACTH and lower cortisol (15$\pm$9.5yo, n=36) [86]. Symptoms correlated with ACTH, 16% with high ACTH, 10% low basal cortisol, 10% with decreased cortisol response to ACTH (7.35$\pm$2.6yo, 3-12yo, n=50) [87]. Higher plasma ACTH in Asperger adults, n=20 [88].

Autonomic nervous system. SNS activity is chronically higher in ASD, as shown by higher basal heart rate, decreased heart rate variability, and blunted skin conductance response [89, 90, 91]. Parasympathetic activity is lower, and respiratory sinus arrhythmia data can predict the severity of repetitive behaviors in 5-10yo [92]. Since CRH triggers SNS activation, these data support chronic CRH release. As noted above, the T*ASD view is that at the time when ASD is diagnosed, CRH release is diminished to chronically activate CRH1 rather than CRH2.

Mast cells, allergies, gut. There is high activation of immune mast cells in ASD [93], and higher prevalence of allergy-related disorders in patients and their siblings [94, 95]. CRH directly activated mast cells, which are involved in allergic responses.

Gut problems are common in ASD patients [96, 94] and their parents [97]. CRH activation of mast cells increases gut permeability [98].

There is general pro-inflammation immune activation in ASD [94], which can be due to CRH but may simply stem from the excessive release of stress-related agents.

Eye gaze. CRH overexpression decreases UCN expression in the EW nucleus, which mediates learned eye gaze [99].

Other. There is high ASD comorbidity with anxiety [100], and maternal post-traumatic stress disorder increases ASD risk [101]. Both point to high CRH.

The cortisol response to ACTH stimulation is slower in ASD [102] and its levels are higher [103], supporting chronic activity.

ASD is associated with skin hyperpigmentation phenomena [104], which are also associated with high ACTH [105]. Recall that melanocortins, which affect skin pigmentation, are a product of the the ACTH gene POMC, stimulated by CRH.

People with ASD have non-brain health problems in most organs, which are the main cause of premature death [106]. This indirectly supports the UCN path, because UCNs are expressed in these organs and are important for their healthy development.

3.2 Anatomical growth

Prenatal. Intrauterine growth restriction (IUGR) is associated with dramatically increased ASD risk [107, 108]. This supports a growth problem in ASD, and specifically supports high CRH, since high late pregnancy maternal plasma CRH is significantly associated with preterm small for gestational age births [109]. UCNs are expressed in the placenta and fetal membranes, and are needed for prenatal glucose uptake [110, 8].

Early postnatal. ASD involves increased excitation-inhibition ratio during early development [111], and decreased lateral inhibition in cortical minicolumns (mean age 12yo) [112]. This shows impaired postnatal synaptic pruning and/or impaired postnatal brain development, which is normally dominated by maturation of inhibition.

Accelerated postnatal head circumference growth is consistently reported in ASD [113, 114, 115, 116, 117] (but see [118]). Baby length was reported to be higher in 4-5 month old boys, with babies at the top 10% of physical size having greater symptom severity later [116]. Babies with ASD show extremely rapid weight gain in infancy [107]. These data support high postnatal ACTH, since ACTH and other POMC products directly promote bone growth [119].

ASD brains show strong local connectivity and low long-distance one [120], with hyper-connectivity at young ages [121], supporting reduced postnatal pruning and development.

Related to sensory hypersensitivity in ASD, there is auditory brainstem pathology, with delayed maturation of low- to high-level pathways [122].

Epileptic seizures are common in ASD. This can be explained by increased brain excitation by CRH (e.g., in the hippocampus), and by reduced development of brain inhibitory interneurons.

3.3 Growth agents & pathways

Glucose. ASD is significantly associated with a family history of hypothyroidism [94], especially with maternal hypothyroidism during pregnancy [123]. Hypothyroidism is associated with hypog, further supporting the association of reduced glucose with increased ASD risk.

Gestational diabetes increases ASD risk [1, 124]. ASD risk is increased with type 1 diabetes and increased blood glucose levels [125, 126]. Using the HOMA-IR model, people with ASD were shown to have insulin resistance and decreased brain glucose metabolism (4-18yo, n=60) [127]. These data show the importance of cellular glucose for opposing ASD.

Neonatal hypog is independently associated with developmental problems and ASD traits [108]. Since UCN secretion is stimulated by glucose, it is decreased in hypog states.

Protein synthesis. The Akt/mTOR growth axis is dysregulated (mainly reported decreased) in ASD [128, 129, 130, 131, 132]. UCNs and GSTRDs are needed for the proper activation of this axis during development.

Glutathione (GSH), which is a major agent promoting protein synthesis in the PPP, is decreased in ASD [133].

ASD is associated with neonatal jaundice [134, 79] (although not consistently [135]). The enzyme G6PD is essential for the pentose phosphate pathway (PPP) and protein synthesis, and neonatal jaundice indicates G6PD deficiency [136] and neonatal hypog [108]. Thus, neonatal jaundice supports reduced cellular glucose in ASD.

3.4 Sex steroids

Androgens. DHEA is increased in ASD, in both prepuberty males and females [137, 138, 139, 140, 141], showing excessive ASTRDs. Note that female androgens are mainly produced in the adrenal gland, where their production is stimulated by ACTH.

Testosterone, estrogen. Although testosterone is mainly reported to be increased in ASD (prepubertal, pubertal and in adults) [142, 143, 144, 145, 138, 146, 139, 147, 148], it is also reported to be decreased [149, 150, 151] or unchanged [152]. The increased DHEA in ASD explains the increased testosterone results. The conflicting results can be explained by reduced GSTRD production due to high ASTRDs.

Both an association with higher amniotic fluid estrogens [153] and no association with umbilical cord testosterone [154] were reported. No relationship between amniotic fluid testosterone and autistic traits was found in girls [155]. There are contradictory reports on the association between prenatal or early postnatal testosterone and autistic traits [156, 157, 158]. Thus, the evidence for a prenatal problem is weak.

Follicle-stimulating hormone and estrogen were reported to be decreased in both male and female ASD serum [159], supporting reduced GSTRDs.

Polycystic ovary syndrome, prenatal androgens. PCOS is a condition involving high ASTRDs, mainly DHEA. Large population studies have shown that children of mothers with PCOS have a higher risk of ASD [160, 161]. Regardless of a PCOS diagnosis, mothers of children with ASD had higher testosterone [162].

As mentioned above, the T*ASD view is that high androgens during sensitive developmental periods increase risk via an association with increased CRH. Prenatal testosterone is released

during weeks 8-20 of pregnancy, so this should be a sensitive period to stress-induced ASD. Indeed, the association of ASD with maternal stress during pregnancy [163, 164] may be specific to this period. An all-Denmark birth cohort showed that maternal hospitalization due to 1st/2nd trimester viral or bacterial infection increases risk about 3x [165], and increased 1st trimester maternal stress during the Quebec ice storm was associated with increased ASD risk [166].

Supporting the effect of stress on sex STRDs, prenatal stress increases anogenital distance (a masculinization index) in human females, with a trend for a decrease in in males [167].

Congenital adrenal hyperplasia (CAH) involves high ACTH and androgens, and is not linked to ASD, at least in girls [155]. These PCOS and CAH data imply that CRH and ACTH are involved in PCOS but not in CAH pathogenesis.

Masculine/feminine features. ASD involves higher gender dysphoria [168], with males and females more likely to be bisexual and homosexual, respectively [169]. In the general adult population, people with autistic traits are more likely to be bisexual or with an uncertain orientation [170]. In addition, women with ASD have more masculine facial features than women without ASD [171, 172, 173], and men with ASD are more feminine in some ways [171, 172] (although hyper-masculine faces were also reported in prepubertal boys with ASD [173]). These data imply lower androgens in males and higher androgens in females during sensitive developmental periods. This accords with T*ASD, because higher CRH-ACTH-DHEA increases androgens in females, and these ASTRDs opposes GSTRDs so decrease the organizational effects of GSTRD androgens in males.

There is also some evidence that CRH decreases ovary aromatase, which converts testosterone to estrogen [174]. This could be another route through which women with ASD have less estrogen and more testosterone than other women.

Endocrine disrupting chemicals (EDCs). Pre- or perinatal exposure to EDCs (e.g., some pesticides, plastics) increases risk [175, 176]. Many EDCs mimic estrogen, amplifying its recruitment of CRH towards the end of pregnancy. (Note that higher postnatal estrogen is relatively protective due to protein synthesis, see above.)

Sexual behavior. CRH1 basally stimulates gonadotropin hormone-releasing hormone (and thus GSTRDs) [177], which might explain the higher sexual drive and frequent inappropriate sexual behavior shown by adolescents and adults with ASD [178].

Summary. ASTRDs are definitely increased in ASD, in both males and females. Testosterone is usually increased in males, and this is most likely due to the increase in ASTRDs. Conversely, GSTRDs are lower in males. Males are more vulnerable in developmental periods in which they need GSTRDs. These data support increased CRH-ATCH and decreased long-term GSTRD plasticity in ASD. Prenatal estrogens increase risk, probably by stimulating CRH.

3.5 Oxytocin

OXT is dysregulated in ASD, with most papers reporting decreased OXT [179, 180], but several reporting an increase [181]. This accords with the T*ASD prediction. The decrease is due to high testosterone [33] and decreased UCN-mediated plasticity [35]. The increase happens because plasticity, including at the hypothalamus, involves maturation of inhibitory interneurons, and possibly because estrogen (which stimulates OXT [67]) is increased due to DHEA. There is also the possibility of inherently decreased OXT capacity in ASD due to epigenetics.

Pitocin usage during labor indicates delivery problems (see above), but may also increase risk by inducing a long-term desensitization of OXT receptors [182]. Usage of the OXT antagonist tractocile during labor is associated with later social communication problems [183].

Several wide cohort studies showed a strong association of ASD with **reduced breastfeeding** [184, 185, 186, 187, 188, 189, 190]. This can be because human milk contains OXT [30], and because breastfeeding is accompanied by longer human touch, which reduces CRH [191] (even beyond puberty [192]) and increases OXT.

There is one report of decreased fMRI activity in the insula following affective touch in ASD, coupled with increased activity in the primary somatosensory cortex following neutral touch [193].

3.6 Food intake

Babies and toddlers later diagnosed with ASD show decreased satiety and increased desire for food intake (non-stop suckling, decreased nursing strike) [194, 195, 196, 197]. In the general population, autistic traits at age 6 years are associated with being hungry/not satisfied, or no breastfeeding, or small drinking quantities at age 2 months [198]. These data can be explained by the fact that part of the role of OXT is to signal satiety and decrease food intake (mainly sugars) [199], so reduced OXT prolongs the time to satiety. Another account is that the deficiency of glucose for growth in ASD is sensed (via an unknown mechanism, although see CRRs below), and this stimulates continued food intake.

Children with ASD show restricted food preference and an unwillingness to try novel food [200]. This may be due to their general avoidance of novelty to prevent higher CRH release.

At later ages, there is high obesity in ASD [21], which could be due to chronically high activation of CRH1, which stimulates the counter-regulatory responses (CRRs) to hypog and food intake [19]. In addition, in ASD, less ingested glucose is channelled to protein synthesis, which leaves excessive blood glucose. In this situation, serotonin promotes the storage of glucose in adipose tissue as fat [201]. Supporting this account, blood serotonin is elevated in patients [202] and correlates with symptom severity [203].

4 Treatment

4.1 Detection

Postnatal levels of blood, urine, saliva, hari and/or CSF CRH, ACTH, cortisol, UCNs, testosterone, estrogen, DHEA/cortisol ratio, and OXT, can be used for early screening. The most promising biomarker may be **ACTH**, because it is directly related to both CRH and ASTRDs. Levels at birth would probably be less informative than levels at the age of 3 months, since at this age adrenal involution, coupled with a dramatic decrease in DHEA, should already have happened. However, as indicated above, there are reports in which adrenal involution occurs much earlier. Normal timelines for CRH and ACTH decrease and adrenal involution should be investigated more in order to devise the optimal detection schedule for ASD. Prenatal (maternal plasma and amniotic fluid) levels, mainly of CRH and ACTH, would be useful too.

Direct demonstration of higher adrenal volume using imaging would also point to a problem, because reduced ACTH is a major factor in adrenal involution [204], with both CRH and ACTH increasing adrenal volume [205].

4.2 Preventive treatment

Is it justified? When discussing preventive treatment, we must keep in mind that so-called 'autistic traits' are part of the vast repertoire of human properties, and are not necessarily a bad thing to have. Nonetheless, it is clear that many people with ASD are simply unable to conduct an independent fulfilling life, which justifies treatment.

Definition. By 'preventive treatment', I mean treatment made during the damage period, since it is generally not possible to reduce high pre- and perinatal CRH. Nonetheless, it may be a good idea not to take certain medications during pregnancy. For example, selective serotonin reuptake inhibitors, which are a very common treatment for depression, are associated with increased 2nd trimester CRH (although causality has not been shown) [206].

Behavioral. A general principle is that drug treatment should be accompanied by behavioral treatment. The problem is impaired brain plasticity (learning), but the brain still has learning capacity, and the impairment can be greatly alleviated by repeated training [207].

Pleasant postnatal human **touch**, and **breastfeeding**, should reduce risk by increasing OXT and reducing CRH in the brain.

CRH, DHT. The best treatment would be to **reduce CRH levels**. Antibodies to CRH have been isolated in mice [208]. However, the main damage is done in the brain. RNA interference methods can be used to reduce CRH production, but the drug needs to penetrate the brain.

There is a promising way to reduce CRH. DHT mediates many of the organizational effects of GSTRD androgens [209]. Probably as part of this role, it suppresses ASTRDs, decreasing HPA axis activity and the release of its driving agents, including CRH and ACTH [210, 211]. DHT synthesis during male minipuberty takes place only in the testis, with adrenal production

being extremely high at birth but dropping to very low levels at 10 weeks [29]. Conversely, ACTH inhibits 5a-reductase, the rate limiting enzyme in DHT production [212].

Thus, **exogenous DHT, which is readily available, could ameliorate or even prevent the ASD phenotype** if used at the right time. DHT is available in transdermal patch form, making its administration to babies very easy.

Obviously, this treatment may be suitable only for males, but males comprise 80% of the ASD population. DHT mediates some or all of its anti-CRH effects via its conversion to 3b-diol (by 3beta-hydroxysteroid dehydrogenase) [210], which binds estrogen receptor beta but not the androgen receptor. Like estrogen, 3b-diol phasically increases OXT [67]. Thus, 3b-diol treatment may be suitable for females (and possibly males as well).

This DHT proposal may seem paradoxical in light of the increased levels of androgens reported in ASD. However, recall that according to T*ASD, these increased levels are mainly due to ASTRDs, not GSTRDs, which are the normal source of DHT during minipuberty.

Other. There are additional possible treatments. Cortisol reduces CRH release, so postnatal **exogenous glucocorticoids (GCs)** might help. GC doses should be lower than those that desensitize the GC receptor (GR).

ACTH suppression (e.g., with somatostatin analogues such as pasireotide) could be helpful, mainly to reduce damage done in the ASTRD. This treatment may need to be supplemented by exogenous GCs.

Exogenous OXT during the first postnatal months might be beneficial. Some intranasal OXT crosses the blood-brain barrier (BBB) [213], but there is no evidence that it reaches the hypothalamus. Blood OXT needs assistance in order to cross the BBB in meaningful amounts and to remain active for more than a short time.

Exogenous UCNs diffuse across the blood-brain barrier [214], and may be beneficial by competing with CRH for receptor binding.

4.3 Symptomatic treatment

ACTH suppression (e.g., with DHT) may be a good treatment for aggression symptoms exhibited after the initial damage period (recall that ACTH and DHEA promote such aggression). Reducing CRH should also counter aversion to novelty and repetitive movements and habits.

5 Discussion

ASD is one of the major brain disorders, and one of the largest mysteries of modern science, medicine and human society. Here I presented the first complete theory of ASD, complete in the sense that it explains the etiology, symptoms, and pathology of ASD, and relies on substantial empirical evidence.

Other theories. At present, there is no theory of ASD that mechanistically explains even its symptoms, let alone its etiology and pathology [215]. Several hypotheses have been articulated

regarding the nature of ASD. The 'extreme male brain' hypothesis [216] posits a difference between systematizing, which is supposedly a male way of behavior, and empathizing, supposedly female. These notions are very hard to define, and in any case do not provide any mechanistic account. T*ASD agrees that females with ASD are more masculine in some ways, but as the evidence brought above shows, males with ASD can be argued to be more feminine than males without ASD.

The idea that OXT is central in ASD has been raised [217], which is natural in light of the role of OXT is social development. However, mechanisms have not been detailed, and although OXT dysregulation exists in ASD, it is clear that OXT is far from explaining the variety of ASD symptoms and properties. In T*ASD, the main downstream event is an impairment in postnatal plasticity due to reduced growth signaling by UCNs and GSTRDs. OXT is one of the main sites of damage.

Another idea is that ASD involves an increased excitation-inhibition (E/I) ratio during early development [111]. This is indeed a plausible outcome of impaired postnatal plasticity, but a detailed review concluded that although excitation and inhibition are altered in ASD, there is no real evidence for the increased E/I theory [218].

A hypothesis with some mechanistic basis is that of aberrant growth pathways such as Wnt, ERK, and Akt [219]. In this idea, ASD begins in prenatal life, with a disruption of proliferation and migration. This follows with a disrupted postnatal brain connectivity. There is an emphasis on risk genes. T*ASD agrees with this hypothesis in the importance of impaired growth pathways, but disagrees with it in their timing and concrete identity, and in the genetic emphasis. In addition, this theory does not include any mechanistic account of the specific symptoms of ASD.

Strengths and weaknesses. T*ASD presents a view of the etiology of ASD that is highly biologically plausible and consistent with the evidence. It mechanistically addresses basically all of the symptoms of ASD, and utilizes all of the salient data gathered about the disorder. It is supported by a substantial body of empirical evidence of different types and modalities. As such, it is a very strong theory. Its greatest weakness at present is that there is no supporting evidence showing that the putative pathways are indeed impaired during the relevant damage period. There is a lot of evidence for the involvement of CRH and sex steroids somewhat after (and before) this period, but not during the first 1-9 postnatal months. In addition, there is very little UCN data.

Genetics. Because ASD occurs due to stress during pregnancy or after birth, T*ASD does not predict meaningful DNA changes. The tendency for increased CRH release (and/or for increased effect on its downstream paths) may be encoded genetically or epigenetically, but this most likely involves a large number of genes and a small effect in each of them. The damage occurs during development, and may not leave any genetic or epigenetic trace in the causal genes, although there is likely a persistent epigenetic change to the CRH system that causes chronic CRH1 activation. Indeed, there are different DNA methylation patterns between disease-discordant monozygotic twins, with a significant correlation between DNA methylation

and ASD traits [220]. Overall, T*ASD generally does not expect supporting genetic evidence. There is some hypothesized genetic data pointing to CRH, CRH2 and UCN3 genes [221], but it is not strong.

Treatment. An exciting aspect of T*ASD is that it points to easy biomarkers (ACTH, ASTRDs, adrenal volume) and to a readily available preventive treatment that's quite easy to administer to babies. Although the definition of what constitutes 'excessive' CRH/ACTH would surely be blurry, many of the more severe cases of ASD most likely involve levels that would be classified as excessive without argument. The proposed treatment may alleviate these cases, while people with ASD traits will not be treated, allowing human diversity.

List of Abbreviations

Terms introduced in this paper are marked by a **bold** font.

ACTH: adrenocorticotropic hormone.
aMSH: alpha-melanocyte stimulating hormone.
ASD : autism spectrum disorder.
ASTRD: adrenal steroid.
BNST: bed nucleus of the stria terminalis.
C-CRH2: CRH-induced CRH2 receptor signaling.
cAMP: cyclic adenosine monophosphate.
CRH: corticotropin-releasing hormone (also CRF, factor).
DHT: dihydrotestosterone.
EW: Edinger-Westphal (nucleus).
GSTRD: gonadal steroid.
DHEA(S): dehydroepiandrosterone (sulfated).
GC: glucocorticoid.
MAPK: mitogen-activated protein kinase.
OXT: oxytocin.
PCOS: polycystic ovary syndrome.
POMC: prooptiomelanocortin.
PPP: pentose phosphate pathway.
SNS: sympathetic nervous system.
STRD: steroid.
T*ASD: the theory of ASD presented here.
U-CRH2: UCN-induced CRH2 receptor signaling.

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