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The biochemical basis and treatment of autism: Interactions between mercury, transsulfuration, and androgens ☆

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Abstract

Impairments in social relatedness and communication, repetitive behaviors, abnormal movement patterns, and sensory dysfunction characterizes autism spectrum disorder (ASDs). It has long been recognized that there is a genetic component to some ASDs, but recent studies have also suggested that some ASDs are triggered by environmental factors. Mercury exposure can cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with ASDs, and recent studies have shown increased body-burdens of mercury in some ASDs. It has also been shown that mercury exposure can trigger a biochemical cyclical pattern of interaction to develop between the transsulfuration and androgen pathways that are directly characteristic with the biochemistry observed in some ASDs, and would be expected to correlate with the behavioral/physical traits associated with or defining ASDs. In light of potential blocks in manipulating the transsulfuration pathway in ASDs, LUPRON® therapy has been utilized for the treatment of androgen abnormalities in ASDs. The use of LUPRON® in a large cohort of ASDs of various ages has been observed to be associated with a significant clinical amelioration in hyperactivity/impulsivity, aggression, self injury, severe sexual behaviors, and irritability behaviors that frequently accompany ASDs.
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Keywords: GnRH; Leuprolide acetate; Precocious puberty; Thimerosal

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Contents

☆ Potential conflict of interest: Dr. Mark R. Geier has been an expert witness and a consultant in vaccine/biologic cases before the no-fault National Vaccine Injury Compensation Program (NVICP) and in civil litigation. David Geier has been a consultant in vaccine/biologic cases before the no-fault NVICP and in civil litigation. Dr. Mark R. Geier and David Geier jointly have a patent pending for the treatment of autistic disorders.

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1. Background on autistic disorders

Autism spectrum disorders (ASDs) are apparently increasingly prevalent neurodevelopmental disorders characterized by impairments in social relatedness and communication, repetitive behaviors, abnormal movement patterns, and sensory dysfunction. Symptoms of ASDs may be present from birth, but in a significant portion of children regression into ASD occurs between 12 and 24 months of age. In addition, ASD individuals have an increased prevalence of gastrointestinal disease and dysbiosis, autoimmune disease, and mental retardation [1]. It has recently been reported that ASDs may presently occur in as many as one in about 85 children, and ASDs affect many more males than females, occurring at a ratio of at least 3:1. It has long been recognized that there is a genetic component to some ASDs, but a number of recent studies have suggested that there are also environmental triggers for ASDs [1,2].

2. Mercury exposure inducing autistic disorders

Overall, in the US widespread exposure to thimerosal-containing pharmaceutical products) and environmental exposure to mercury (mercury vapor and methylmercury) resulted in infants routinely receiving doses of mercury in some cases >350 total micrograms (μg) of mercury during the first 6 months of life, that were in excess of the US Environmental Protection Agency (EPA), the US Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) mercury safety limits for important neuronal developmental periods during the first year of life [3]. Researchers have reported that mercury exposure can cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with ASDs, and the similarities extend to neuroanatomy, neurotransmitters, and biochemistry [1,2,4]. Faustman et al. concluded, "…mercury exposure altered cell number and cell division; these impacts have been postulated as modes of action for the observed adverse effects in neuronal development. The potential implications of such observations are evident when evaluated in context with research showing that altered cell proliferation and focal neuropathologic effects have been linked with specific neurobehavioral deficits (e.g., autism)" [5]. In previous epidemiological studies mercury exposure was significantly associated with ASDs [1,2,6–10]. Additionally, Hornig et al. showed that low-dose mercury administration at specific postnatal periods induced autistic symptoms in a susceptible mouse strain characterized by autoimmunity [11]. The autistic symptoms included: growth delay, reduced locomotion, exaggerated response to novelty, increased brain size, decreased numbers of Purkinje cells, significant abnormalities in brain architecture affecting areas sub-serving emotion and cognition, and densely packed hyperchromic hippocampal neurons with altered glutamate receptors and transporters.

3. Biological markers of elevated mercury body-burden toxicity in autistic disorders

In evaluating the body-burden of mercury following exposure to mercury, it has been observed that significant mercury concentrations can persist, particularly in the brain, for a long time following exposure [2]. It was observed that infant monkeys receiving low-dose organic mercury exposure resulted in a significant concentration of mercury present in the brain. Furthermore, it was determined following entry of organic mercury into the brain, there was a conversion of the organic mercury to inorganic mercury, and that the inorganic mercury in the brain was found to persist with no significant decrease in concentration 120 days following exposure [12].

In evaluating mercury body-burdens in ASDs, Bradstreet et al. evaluated urinary heavy metal concentrations among 221 children with ASDs to 18 age- and gender-matched neurotypical controls following chelation therapy with *meso*-2, 3-dimercaptosuccinic acid (DMSA). It was observed that there were approximately 3-times significantly greater urinary mercury concentrations among autistics relative to controls, whereas autistics and controls had similar urinary concentrations of other heavy metals [13]. Additionally, in a case-series of ASD patients, significant mercury concentrations were observed in urine, fecal, or hair samples following chelation therapy [1]. Likewise, Holmes et al. examined first baby haircuts and determined that a group of 94 autistics had significantly higher body-burdens of mercury in comparison to 45 age- and gender-matched non-autistic controls by demonstrating that the ability to

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excrete mercury in first baby haircuts was inversely proportional to the severity of autistics [2]. On the whole, the ability of autistics to excrete mercury was very low compared to non-autistic matched controls. Other researchers have examined urinary porphyrins among several large ASD cohorts in comparison to controls [14,15]. It was observed that there were 2- to 3-fold significantly increased concentrations of urinary porphyrins specifically associated with mercury (i.e. precoproporphyrin, pentacarboxyporphryin, and coproporphyrin) among autistic individuals in comparison with controls, with >50% of autistics having urinary coproporphyrin levels more than 2 standard deviations above the control mean level of urinary coproporphyrin. Furthermore, it was observed that increasing clinical severity of ASDs was correlated with increasing urinary porphyrins, and that chelation significantly reduced the urinary porphyrin levels observed among autistic individuals.

4. Transsulfuration and androgen pathway markers in autistic disorders

In considering mercury toxicity, mercury binds to cysteine thiol (-SH) groups on intracellular proteins and inactivates their function. The cysteine-SH group of glutathione binds mercury and protects essential proteins from functional inactivation. The synthesis of glutathione has been directly linked to the role of mercury excretion [16] and cellular protection from mercury induced damage [17]. Thus, individuals with lower glutathione levels would be more sensitive to the adverse effects of mercury [2].

Several recent studies have examined blood markers in the transsulfuration pathway in ASDs. It was shown based upon examination of several hundred individuals with ASDs that they have significant reductions in cysteine, sulphate, total glutathione, and reduced glutathione (i.e. active glutathione that can bind mercury) and significant increases in oxidized glutathione (i.e. inactive glutathione that cannot bind mercury) in comparison to controls [1,18–20]. Furthermore, recent epidemiological studies have associated genomic susceptibility factors in mercury detoxification pathways with ASDs [20–23].

In also considering mercury toxicity, it has been observed that mercury toxicity is exacerbated by androgens whereas estrogens ameliorate mercury toxicity, and as a result males are significantly more susceptibility to mercury poisoning than are females. This phenomena has been observed in tissue culture, in animal models, and in human mercury poisonings [2,16,24]. Additionally, it was observed in testicular tissue culture and in human exposure to low-dose mercury resulted in increased testosterone levels [25,26].

Several studies have examined androgen levels among ASDs. It has been observed that individuals with ASDs had significantly increased pre- and postnatal levels of testosterone and other androgen metabolites, and that clinically increasingly severe ASDs were correlated with increasing testosterone levels [1,18,27,28]. Furthermore, it has been reported that androgen levels are inversely correlated with behaviors that, in the extreme, would count as diagnostic symptoms for ASDs including: eye contact, vocabulary development, social functioning, and narrow interests, and there is preliminary evidence of somatic hypermasculinization in autistic disorders [18,27–29].

5. Transsulfuration and androgen pathway interactions in autistic disorders

The basis for the transsulfuration and androgen pathways to interact stems from the fact that a critical regulatory step in the androgen pathway involves the regulatory metabolite, dehydroepiandrosterone (DHEA). DHEA can either be converted further down the androgen pathway towards testosterone by being converted to androstenedione or androstenediol, or towards the normally favored storage molecule, dehydroepiandrosterone-sulfate (DHEA-S). The conversion of DHEA to DHEA-S by the enzyme hydroxysteroid sulfotransferase (HST) is dependent upon sulphation, requires glutathione as a co-factor, and the enzyme has been shown to be directly inhibited by mercury [30]. Since, individuals with ASDs have been found to have significant decreases in cysteine, sulphate, total glutathione, and active reduced glutathione, as well as increased body-burdens of mercury, there may be a marked shift toward DHEA, and subsequent metabolites in the androgen synthesis pathway. The apparent result, as demonstrated in ASDs, is significantly increased DHEA levels [18] and significantly lowered DHEA-S levels relative to controls [31]. Additionally, HST was shown to be necessary for appropriate function of bile salts [32]. As a result, given the aforementioned abnormalities observed in ASDs, this may contribute to malabsorption and the high prevalence of gastrointestinal disease found in ASDs.

Furthermore, it has not only been shown that transsulfuration metabolites play a critical role in the androgen synthesis pathway, but testosterone, and possibly other androgen metabolites, may have a negative impact on the transsulfuration pathway. A series of animal studies demonstrated that testosterone administration at least partially blocks the conversation of homocysteine to

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cystathionine, whereas estrogen administration had the opposite affect [33,34]. Additionally, researchers showed significant positive correlations between homocysteine and androstenedione levels and glutathione and DHEA-S levels in humans [35]. Thus, it is expected that high androgens would block the transsulfuration pathway. The apparent result, as demonstrated in ASDs, is significantly increased homocysteine, *S*-adenosylhomocysteine (SAH), or adenosine levels in comparison to controls [19,20,36].

In putting these pieces together, it means given the ability of mercury to bind and inactivate glutathione, and given the ability of mercury to inhibit HST directly, that mercury exposure can trigger a biochemical cyclical pattern of interaction to develop between the transsulfuration and androgen pathways that is directly characteristic with the biochemistry observed in ASDs, and would be expected to correlate with the behavioral/physical traits associated with or defining ASDs. Fig. 1 illustrates the interactions between the transsulfuration and androgen pathways [18].

6. Treatment of autistic disorders

Considering the fact that hyperactivity/impulsivity, aggression, self injury, severe sexual behaviors, and irritability are disruptive behaviors that frequently accompany ASDs, psychostimulants and atypical antipsychotics have been used with some success to manage ASDs, but neither drug group is fully satisfactory and clinical response to the stimulants varies. Because of potential side effects and limited clinical responses to present drugs, it has been suggested that more research is needed on the management of all of these target symptoms by new drugs [37]. Given the present understanding of the biochemical processes involved in ASDs, one can design entirely new treatment regiments for ASDs that directly address these biochemical variations.

Given the potential for blocks in the transsulfuration pathway, an appropriate starting place for considering the biochemical variations in ASDs is to address their androgen problems. This is because many of the behavioral aspects of ASDs are the apparent result of increased androgens and because there are presently available drugs that have a long track record of being able to significant lower androgen levels with minimal other systemic adverse effects on the body [27].

In the course of reviewing various potential candidate anti-androgen drugs for the treatment of ASDs, it was determined that LUPRON® (leuprolide acetate, TAP Pharmaceuticals) was an appropriate choice. LUPRON®

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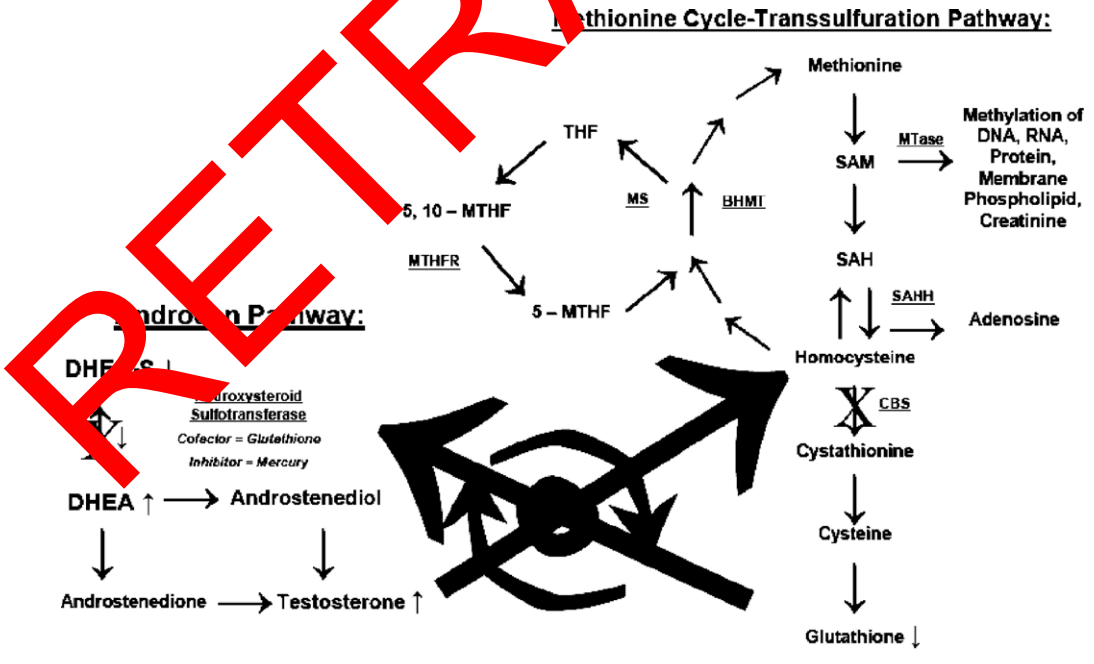

Fig. 1. A summary of the interaction between the transsulfuration and androgen pathways in autistic spectrum disorders [18]. BHMT = Betaine Homocysteine Methyltransferase. MS = Methionine Synthase. SAM = *S*-adenosylmethionine. MTase = Methyltransferase. SAH = *S*-adenosylhomocysteine. CBS = Cystathionine β-Synthase. THF = Tetrohydrofolate. 5-MTHF = 5-Methyltetrahydrofolate. 5, 10-MTHF = 5, 10-Methyltetrahydrofolate. SAHH = SAH Hydrolase. DHEA-S = Dehydroepiandrosterone-sulfate. DHEA = Dehydroepiandrosterone.

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t1.1 Table 1

t1.2 Examples of clinical outcomes observed in patients with autism spectrum disorders following LUPRON® therapy

t1.3	Patient	LUPRON® Dosing	Observations
t1.4	18 year-old male Caucasian diagnosis: autism	15 mg IM Depot (28 days) 0.2 mL SQ (everyday), gradually increased to 0.5 mL SQ (everyday)	Pre-treatment: ATEC: overall impairments=80–89th percentile, speech/language/communication=30–39th percentile, sensory/cognitive/awareness=40–49th percentile, health/physical/behavior=90–99th percentile, and sociability=70–79th percentile. Extreme aggressive behaviors including being destructive, violent, and was reported to hit and injure himself and others. Patient has sexual behaviors (su masturbation).
t1.5			Treatment (day 156): ATEC: overall im ments= 39th percentile, speech/language/commun tion=30–39th rcentile, sensory/cognitive/awareness=30–39th rcentile, healt physical/behavior=70–79th p ntile, a sociability 0–59th percentile. Parents and edu ors reported m im vements in attention, cognitive a reness, re ptive lang e skills, and especially reduced level aggr ve behaviors. Reduction of self-mutation and ysical ence toward thers. Patient has had a significa eduction in sexual haviors (such as masturbatio patient still su from mood swings and occasional sleep pro ms.
t1.6	11 year-old male Caucasian, diagnosis: autism	15 mg IM Depot (28 days) 0.4 mL SQ (everyday), gradually increased to 0.7 mL SQ (everyday)	Pre-treatment: ATEC: all impairments=80–89th percentile of verity), speech/langua /communication=70–79th percentile, nsory/cognitive/awareness=50–59th percentile, health/ hysical/behavio 80–89th percentile, and sociability=60–69th rcentile. Patie had a bone age consistent in age with a 14 5 year-old atient has body hair (since 9 year-old) and sexua ors (such as masturbation since 9 year-old).
t1.7			Treatment (day 104): ATEC: overall impairments=40–49th per e, speech/language/communications=60–69th percentile, sensory/cognitive/awareness=40–49th percentile, health/physical/behavior=60–69th percentile, and sociability=20–29th percentile. Parents and educators reported major improvements in attention, cognitive awareness, and receptive language skills. Patient has had a significant decrease in body hair and sexual behaviors (such as masturbation).
t1.8	9 year-old male African American, diagnosis: PDD-NOS	IM Depot (28 ys) 0.5 mL SQ, gradua increased to 0 mL SQ (every)	Pre-treatment: ATEC: overall impairments=20–29th percentile of severity), speech/language/communication=20–29th percentile, sensory/cognitive/awareness=40–49th percentile, health/physical/behavior=20–29th percentile, and sociability=40–49th percentile. Patient has body and facial hair (since 5 year-old), body odor (in the last year), sexual behaviors (such as erections and advanced genital development).
t1.9			Treatment (day 58): ATEC: overall impairments=0–9th percentile, speech/language/communications=0–9th percentile, sensory/cognitive/awareness=0–9th percentile, health/physical/behavior=0–9th percentile, and sociability=0–9th percentile. Parents and educators reported major improvements in attention, cognitive awareness, and receptive language skills. Patient has been observed to take a very active interest in the world around him. Patient has had a significant decrease in body and facial hair, body odor, and sexual behaviors (such as erections and genital development).

t1.10 Pervasive developmental delay–not otherwise specified = PDD–NOS; intramuscular = IM; subcutaneous = SQ.

The Autism Treatment Evaluation Checklist (ATEC) Form was developed by the Autism Research Institute (San Diego, California). The ATEC consists of 4 subtests: Speech/Language/Communication (14 items — scores can range from 0–28), Sociability (20 items — scores can range from 0–40), Sensory/Cognitive/Awareness (18 items — scores can range from 0–36), Health/Physical/Behavior (25 items — scores can range from 0–75), The Autism Research Institute calculates four subscale scores and a total score (total scores can range from 0–180) from the ATEC form. The scores are weighted according to the response and the corresponding subscale. The higher the subscale and total score, the more impaired the subject. The lower the subscale and total score, the less impaired the subject. The ATEC can also be used to monitor the effectiveness of treatment (such as the

t1.11 treatment regimens described herein) of a subject suffering from autism or an autism spectrum disorder.

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is a gonadotropin-releasing hormone (GnRH) agonist that binds to GnRH receptors in the hypothalamus. As a result, LURPON® will down regulate the production of luteinizing hormone (LH) and follicle stimulating hormone (FSH) in the pituitary, and hence reduce production of androgens. LUPRON® is a FDA approved drug for use in pediatric patients with premature puberty, and in other conditions in adults such as prostate cancer or endometriosis where it is crucial to control androgen levels. LURPON® has been shown to significantly reduce androgen levels in children with premature puberty [38]. LUPRON® has been on the US market for many years, and it has been reported that long-term LUPRON® treatment of children with premature puberty had no long-term adverse effects on reproductive function [39]. Furthermore, leuprolide acetate administration was previously reported to significantly improve behavioral outcomes in ASDs [40].

In our clinical experience we have observed that LUPRON® administration to nearly 100 individuals with ASDs significantly lowered androgen levels and has resulted in very significant overall clinical improvements, with few non-responders to the therapy. Table 1 summarizes three representative examples of patients with ASD from different age groups that were drawn from our LUPRON® treated ASD patients. In our experience LUPRON® administration has been found to be associated with minimal adverse clinical effects in ASD patients.

7. Conclusion

It is clear that while some ASDs have a genetic component, based upon the presently available scientific evidence, it is apparent that mercury exposure can play a causal role in some ASDs. There is clinical evidence to support increased body burdens of mercury in ASDs, and there is also biochemical and genomic evidence supporting specific factors that would make some individuals with ASDs particularly susceptible to mercury toxicity. Based upon an understanding of the apparent biochemical processes occurring in ASDs, namely that they have significantly reduced metabolites in the transsulfuration pathway and significantly increased metabolites in the androgen pathway, we have successfully utilized LURPON® therapy to treat a wide variety of patients who presented with ASDs.

Take-home messages:

- It has long been recognized that there is a genetic component to some autistic disorders, but a number of recent studies have found evidence of mercury toxicity in autism.
- Widespread exposure to ethylmercury (Thimerosal-containing medicinal products) and environmental exposure (mercury vapor and methylmercury) have resulted in many infants in the US receiving total cumulative doses in excess of safety guidelines.
- Autistics have been demonstrated to have genetic, biochemical, and hormonal susceptibilities to mercury toxicity.
- Mercury exposure can trigger a biochemical cyclical pattern of interactions to develop between the transsulfuration (low metabolites) and androgen (high metabolites) pathways that is directly characteristic of the biochemistry observed in ASDs, and would be expected to correlate with the behavioral/physical traits associated with or defining ASDs.
- Lowering androgens in autistic disorders with LUPRON® has been shown to correct abnormal androgen levels and result in significant clinical improvements in many patients with autism.

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