Comparing the Pharmacology, Neurophysiology, and Behavior of Prenatal Nicotine Exposure to Attention Deficit Hyperactivity Disorder

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Introduction

Attention deficit hyperactivity disorder (ADHD) is a childhood behavioral disorder characterized by impulsivity, inattention, and hyperactivity that influence one's ability to concentrate and regulate behavior. Children with ADHD are more likely to encounter academic difficulties, such as scoring poorly on exams and withdrawing prematurely from school. 5-10% of all school-aged children are diagnosed with ADHD, and diagnosis of this disorder has increased by 66% over the past ten years alone (Galéra et al, 2011). This disorder is controversial due to disagreements over its diagnostic criteria, its frequency of diagnosis, and its method of treatment. Currently, multiple models exist to explain the underlying cause of ADHD, thus diagnosis is not consistent and includes a broad set of subjective behavioral criteria. This ineffective method of diagnosing ADHD has led to numerous misdiagnoses, rising medical costs, and over-prescribed medications, which can cause harmful side effects in patients.

To better understand the neurobiology of this disorder, scientists have recently adopted the use of animal models. Through animal models, scientists can directly measure which areas of the brain are active when animals show these symptoms, identifying which brain areas might be responsible for these behaviors in humans. However, the scientific community has yet to agree upon a single experimentally validated animal model of ADHD. Many proposed models exist, but none has met all validation criteria. Such a model is needed to examine the effectiveness and long-term consequences of pharmacological treatments. Developing animal models of ADHD is difficult due to the combined genetic and environmental causes of ADHD. However, several studies correlate prenatal nicotine exposure in children to ADHD and other behavioral deficits

later in life. Fetal nicotine rats could be used to further study the neurological basis of ADHD if this model were thoroughly validated.

Maternal smoking is correlated with higher rates of child diagnosis of ADHD and other behavioral disorders. Several studies have found correlations between maternal smoking during pregnancy and behavioral deficits in children, including ADHD (Thapar et al., 2003; Wasserman et al., 2001). Through animal model research, nicotine has been implicated as causing these disorders via long-term changes to a child's brain and behavior (Ajarem & Ahmad, 1998). Nicotine is a teratogen that crosses the placental blood barrier and disrupts fetal development of central neurotransmitter systems, including dopaminergic and monaminergic systems (Slotkin et al., 1987; Navarro et al., 1989; Oliff & Gallardo, 1999). Prenatal nicotine exposure (PNE) causes a multitude of neurochemical changes, including reduced DNA synthesis, altered neurotransmitter function and cortical morphogenesis (Wickström, 2007). These changes occur during critical periods of neonatal brain development, leading to changes in brain area volumes, firing patterns, neurotransmitter concentrations, and receptor density. These alterations are present in areas responsible for impulse inhibition and cognitive focus, leading to behavioral deficits in children. This developmental path matches that of ADHD, making it a good candidate for an animal model of the disorder.

The purpose of this paper is to review the literature about the neurobiological, behavioral, and pharmacological deficits that are seen in ADHD and in PNE. First, I will examine the correlation between PNE and ADHD diagnosis and behavior, including counterarguments to the hypothesis that PNE in children is a predictor of ADHD diagnosis. Second, I will examine the physiology and neuroanatomy of PNE and ADHD, specifically examining the nicotinic acetylcholinergic receptor (nAchR), which is bound by nicotine and vital in neural development,

and two dopamine receptors (D2 and D3) and the dopamine transporter (DAT), which are downregulated in behavioral disorders. Finally, I examine two PNE models of ADHD and suggest how further research could validate PNE as an animal model of ADHD.

Prenatal Nicotine Exposure as a Predictor for ADHD Diagnosis

Many studies have shown that fetal nicotine exposure is correlated with ADHD (Nomura et al, 2010). There is a positive correlation between the magnitude of nicotine exposure and the severity of attentional control (Motlagh et al, 2011; Schmitz et al, 2006) and hyperactivity-impulsivity (Langley et al, 2007) symptoms in children with ADHD. Furthermore, children diagnosed with ADHD who were exposed to nicotine prenatally are more likely to have higher ADHD symptom scores and be less responsive to symptom intervention (Vujik et al, 2006). This correlation appears even when controlling for socioeconomic status, parental IQ, and parental ADHD status (Milberger et al, 1998; Biederman et al, 2009; Mick et al, 2002). One study found that adjusting for these three common confounding factors reduces the increased risk of ADHD diagnosis from three-fold to two-fold, whereas adjusting for other potential confounding factors, including parental age, low birth weight, preterm delivery, low Apgar score, and comorbidity with other conduct disorders does not change the risk increase (Linnett et al, 2005). Granted, these studies only examine children already diagnosed with ADHD and analyze self-reported past smoking habits, but several longitudinal studies have demonstrated that children born to smoking morthers were more likely to be diagnosed with ADHD, further demonstrating the correlation (Romano et al, 2006; Galéra et al, 2011).

One meta study which examined twenty-four studies assessing the relationship between prenatal exposure to nicotine and the risk of developing behavioral problems related to ADHD

found that, in spite of inconsistencies, maternal consumption of tobacco during pregnancy was conclusively correlated with higher ADHD risk. The same study found that ADHD risk results from other maternal lifestyle factors, including alcohol and caffeine consumption and psychological stress during pregnancy, were too inconsistent to draw results from, although this analysis was limited by their small sample of studies (Linnet et al, 2003). Additional meta-analysis of environmental teratogens on behavioral deficits have drawn similar conclusions (Langley et al, 2005).

Confounding Factors in Predicting Increased Risk

A 2009 study examining maternal and paternal smoking habits as linked to attention deficits found that paternal smoking serves as a proxy for genes that contribute to attentional deficits, and that maternal smoking and child attention deficits are not linked (Atlink et al, 2009). This study is useful in suggesting that genetic factors also be examined, as parental smoking may be caused by a genetic predisposition to impulsive behavior. However, this result cannot lead to the conclusion that maternal smoking does not cause attention deficits, as their sample contained a low percentage of mothers who smoked, and of those who smoked, only 2.5% smoked 10 or more cigarettes per day during pregnancy. Greater daily exposure to nicotine during pregnancy was linked with a higher attentional deficit in their children. This extends the hypothesis that children prenatally exposed to 20 cigarettes or more a day will reach a threshold of nicotine exposure that will significantly increase their likelihood.

Other studies have found similar results that the link between maternal smoking and ADHD diagnosis in their children is confounded by other environmental and genetic factors (Braun et al, 2006). Still, the pharmacology of both conditions of both conditions is remarkably

similar, and causal relationships have been established between PNE treatment and behavioral and physiological abnormalities in mice.

Pharmacology

During prenatal neural development, acetylcholine binds nAchR, stimulating dopamine release. This dopamine guides neurons to divide, differentiate into their specialized cell type, and migrate to their permanent location. However, nicotine also binds to the nAchR, which means that when a child is exposed to nicotine during gestation, the child's neurons are guided improperly. Furthermore, this overstimulation of nAchR leads to a dopamine deficit later in development. Dopamine is important for executive control in the prefrontal cortex, leading to problems with attention, impulse control, and hyperactivity, all symptoms of ADHD.

nAchR

Prenatal nicotine exposure changes the expression of the nicotinic acetylcholinergic receptor (nAchR) in areas of the brain involved in dopamine neurotransmission. One 2005 study examined the midbrain dopaminergic reward pathway in post-natal day 14 rats following prenatal nicotine exposure. This area is homologous to the dopaminergic reward pathway, or mesoaccumbens, in humans. Their binding assay found that this exposure reduced nAchR activity in the nucleus accumbens (NAcc), prefrontal cortex (PFC), ventral tegmental area (VTA), and substantial nigra (SA). Furthermore, their mRNA assay found decreased expression of nAchR mRNAs in the VTA for all receptor subtypes and in the NAcc and the PFC for one subtype of the receptor (Chen et al, 2005). Another study found similar results when measuring nAchR mRNAs in the thalamus, hypothalamus, and basal forebrain, areas responsible for

wakefulness and arousal (Frank et al, 2001). Findings from these two studies demonstrate that nAchR is downregulated in the dopaminergic reward pathway in rats prenatally exposed to nicotine and humans diagnosed with ADHD, suggesting a correlation in neurophysiology between the two conditions.

Interestingly, the opposite effect is observed in subjects exposed as adults to nicotine. Research has shown that smokers at autopsy have a higher density of nAchR than non-smokers (Benwell et al, 1988). In addition, study which exposed rats to a daily dose of cigarette smoke found that nAchR was expressed in higher densities in the cortex, striatum, and cerebellum in exposed rats than in control rats (Yates et al, 1995). This is the opposite of what is expected, as under normal conditions, subchronic exposure to an agonist should downregulate expression of the receptor. However, multiple studies have shown that nAchR subtype mRNA expression does not change in response to nicotine exposure (Peng et al, 2004). Thus, it would appear that this upregulation is mediated through post-translational mechanisms only. This corroborates the findings of the Chen et al. study, suggesting that nAchR is indeed downregulated, although its receptors are not.

DAT & D2/D3

Dopamine receptor and transporter downregulation in ADHD can mostly be explained by genetic factors. ADHD is highly heritable, as demonstrated by family, twin, and adoption studies yielding estimates around 76% heritability. The genes implicated in the etiology of ADHD are dopamine receptor genes DRD4 and DRD5, dopamine transporter gene DAT, dopamine beta-hydrozylase gene DBH, serotonin transporter gene 5-HTT, serotonin receptor gene HTR1B, and t-SNARE gene SNAP-25 (Faraone et al, 2005). However, these genes do not fully explain the

phenotypic manifestation and developmental course of the disease, suggesting an environmental interaction. Although some dopamine receptors and transporters are down-regulated in ADHD, an examination of genes for these receptors (DRD4 and DRD5) and transporter (DAT1) show no gene x environment interaction with maternal smoking significantly correlated with ADHD symptoms (Langley et al, 2008). Thus, this would suggest that D2 and D3 downregulation can be explained by environmental factors.

The results of this study match those of a human Positron Emission Tomography (PET) study, which found that dopamine type 2 and 3 (D2 and D3) receptors were less expressed in the accumbens, midbrain, caudate, and hypothalamus of children with ADHD than in those of controls. The study further found that the dopamine transporter (DAT) was downregulated in the midbrain of subjects with ADHD. The amount of downregulation of the dopamine receptors and transporters was correlated with the amount of attentional deficits demonstrated by the subject (Volkow et al, 2009). The same patterns of downregulation were further found in rats treated with PNE (Slotkin et al., 1987).

PNE as an Animal Model of ADHD

A1998 study by Ajarem and Ahmad first proposed that a fetal nicotine model be used for exploring behavioral disorders. The researchers administered nicotine to pregnant mice via injections and examined the pups' righting reflex, cliff avoidance, rotating reflex, locomotion, and anxiety, all measures for motor and cognitive development. Body weights for both control and nicotine-exposed rats showed no significant differences, yet both the rotating and righting reflexes of the nicotine-exposed mice were significantly delayed, showing motor delays. Furthermore, PNE mice were more active in the locomotion task, suggesting increased

hyperactivity, a symptom of ADHD. Since mice have brain areas controlling motor skills and cognition that are homologous to those in humans, this article suggests that prenatal exposure to nicotine in humans would retard growth during a critical prenatal period of brain development, and that this delay could not be explained by differences in birth weight, which is often used as a predictor for ADHD diagnosis. The study further identified nicotine as the causative agent in cigarettes that lead to behavioral deficits (Ajarem & Ahmad, 1998).

A recent study by Zhu et al took a similar approach to propose the PNE mouse as an animal model of ADHD. Brain imaging research has found that the dorsal prelimbic prefrontal cortex (dPL PFC) controls executive functions such as focus and that the anterior cingulate cortex (ACC) controls cognitive functions such as reward anticipation (Bennett et al., 2009). Animal research has found that rats who present ADHD-like symptoms have reduced volumes of and dopamine deficits in brain structures homologous to the ACC and dPL PFC. The behavioral component of Zhu et al's study found that PNE mice were more hyperactive, suggesting that they had an executive control dysfunction. The physiology component found dopamine deficits in the ACC and a smaller ACC volume, suggesting that they had a delay aversion dysfunction. Furthermore, Zhu et al administered methylphenidate and found that it decreased hyperactivity and increased dopamine in the ACC, which is the pathway this drug takes to improve behavior in children with ADHD. This animal model article presents a potential pathway for ADHD development, demonstrating that prenatal nicotine exposure is a possible cause for the cognitive dysfunction subtype of ADHD. However, the article has not presented a fully validated model of ADHD as it claims. Zhu et al only examined one symptom of ADHD and measured hyperactivity just once with no treatment and once after methylphenidate treatment. Nonetheless, it gives direction for the road ahead (Zhu et al., 2012).

Future Directions

Although there is no perfect model of ADHD, prenatal nicotine exposure has been linked to ADHD and other impulsivity disorders, and has started to gain acceptance because of its striking parallels to ADHD at behavioral, neuroanatomical and neuropharmacological levels, and its responsiveness to methylphenidate treatment. In fact, a recent study has shown that children born to mothers who smoke cigarettes during pregnancy showed symptoms of ADHD that are indistinguishable for the ADHD symptoms from other etiologies (Biederman et al., 2012). Despite the growing number of research on impulsivity disorders such as ADHD, the neurophysiological mechanisms that mediate them remain to be determined in large part because no one has examined neural correlates of behavior in appropriate animal models; a situation that hampers the emergence of the translation of science of ADHD and impulsivity.

Animal models of impulsivity disorders are critical because we can control developmental, genetic, and environmental circumstances which are thought to impact behavior and neural deficits observed in these types of disorders. Even if an animal model is not directly related to ADHD, behavioral and brain deficits observed to be similar and will provide insights into how the brain governs inhibitory control and prescription drugs act. Only animal models can provide experimental evidence for the underlying physiology by causing an underlying dysfunction through treatment such as prenatal nicotine and determining a causal relationship to the behavior and neurobiology seen in humans. Because animal models are in controlled environments, they cannot demonstrate disorder progression as would studying a child interacting with his or her parents. Similarly, since we have yet to prove whether or not animals can reason abstractly, we must assume that they are driven to perform tasks by an evolutionary drive to survive rather than an intrinsic motivation to improve themselves. In addition, it is clear

that there is no one underlying cause of ADHD, so all avenues of investigation should be explored to push the field forward. Still, the clear causal link between PNE and ADHD and its already examined use as an animal model for the disorder demonstrate that the PNE model has the potential to be a valid clinical animal model.

Currently, no neurological basis for ADHD exists that is well-established and experimentally verified. A complete neurological basis would explain how the conditions that cause ADHD change neural connections and neurotransmitter concentrations, how these brain area anomalies cause behavioral deficits, and how these deficits are corrected by drugs like methylphenidate. Much of current ADHD research examines this neurobiology on an anatomical scale. Research focused on examining the neural basis on ADHD on a finer scale, such as at the level of the individual neuron, would establish a strong causal basis by revealing the neural mechanism behind the disorder and its pharmacological treatment. This could be achieved by single-unit recordings, or measuring neural firing and neurotransmitters of individual neurons. This research would allow doctors to use imaging to diagnose if a patient has ADHD, reducing misdiagnoses, and allow pharmaceutical companies to target their drug to specific regions of the brain, making the drug more effective while reducing side effects. Focused research in the neural basis of ADHD will help create a concrete method for diagnosing this disorder and how to treat it, improving the outlook for millions of children worldwide.

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