CAPSTONE

Effects of neonatal methamphetamine exposure

Shelby Brock

Introduction

Methamphetamine (MA) is an addictive stimulant which is increasingly abused in 18-25-year-olds in the United States.[1] While it is available pharmaceutically to treat attention-deficit/hyperactivity disorder (Desoxyn), MA is primarily illicitly produced and distributed.[2] Of the 1.9 million users in the US, estimates suggest the prevalence of MA use in pregnancy ranges from 0.7 to 4.8%.[2,3] In 2006, about 24% of pregnant women seeking treatment for substance abuse listed MA as their primary substance.[4] Some studies report conditions seen in MA-exposed neonates including premature birth, low birth weight, decreased arousal, and birth defects such as a facial cleft or gastroschisis, a condition where a hole in the abdominal wall forces the bowel to develop externally.[5,6] While the effects of MA are relatively well-documented (and explored in this review), the mechanisms that facilitate these processes are difficult to study in humans due to confounding variables such as polysubstance abuse, lack of prenatal care, and poverty.[7] Rodent studies provide a solution to this dilemma by allowing control over these variables.

In human adults, MA stimulates the release of monoamine neurotransmitters like dopamine, serotonin, and norepinephrine.[8] With chronic use, MA reduces overall levels of dopamine transporter and causes dysfunction in the striatum and prefrontal cortex of users. As a result of MA exposure in utero, a decrease in striatal dopamine and dendritic spine formation has been observed in rodents, which is consistent with what is known about dopamine dysregulation in humans. In human adults, MA stimulates the release of monoamine neurotransmitters like dopamine, serotonin, and norepinephrine.[8] With chronic use, MA reduces overall levels of dopamine transporter and causes dysfunction in the striatum and prefrontal cortex of users. As a result of MA exposure in utero, a decrease in striatal dopamine and dendritic spine formation has been observed in rodents, which is consistent with what is known about dopamine dysregulation in humans. Studies dating from the 1980s began shifting the focus from prenatal cocaine exposure to MA. For example, cocaine use in pregnancy has been cited as identical to MA exposure, but cocaine has also been shown to cause secondary withdrawals at 4 to 6 weeks of life.[9] Newer studies have aimed to differentiate the effects of MA exposure from other drugs (per self-report), as in Sowell et al.'s alcohol control study and Smith et al.'s longitudinal study of polydrug exposure on development.[5,10]

Infant development, environment, and lifestyle (IDEAL) studies and also correlates

A great deal of human research on MA exposure aims to understand the populations affected and conditions at birth and later in life. The Infant Development, Environment, and Lifestyle (IDEAL) study by Smith et al. is a collection of data from a multi-site longitudinal cohort study which follows up on thousands of mothers and children up to 7.5 years after birth and focuses on how drug abuse affects the life outcomes of exposed children.[5,11,12,13] The data from this study set a baseline for researchers, allowed for future analysis of different aspects of the same data,

and is unique because it screened about 35,000 mother-child pairs and reported the frequency of substance use throughout pregnancy. The original IDEAL study by Smith et al. in 2006 found that the incidence of a child being born as small for gestational age (SGA) was 3.5 times higher in MA-exposed babies.[5] This is concerning because SGA indicates an increased risk for neonatal mortality and morbidity, and one study even suggests that it is associated with lower intelligence, academic difficulties, and behavioral problems.[14] However, it is worth noting that the growth of SGA children typically catches up to their unexposed peers by about 3 years of age.[5] A follow-up analysis by the same IDEAL study team in 2008 found that MA-exposed children were more likely to exhibit decreased arousal and increased central nervous system stress, as determined by the NICU Network Neurobehavioral Scale (NNNS).[11] Not surprisingly, all significant findings from the data were most pronounced in children exposed to MA at least three days per week in utero, which is considered "heavy use." This suggests that the severity of neonatal complications is determined by the amount of exposure to the drug, but the presence of complications is indeed associated with exposure itself.

Participant data from the IDEAL studies are available for other researchers to conduct their own studies. Abar et al. followed up on IDEAL participants for up to 6.5 years after birth to assess cognitive function and early adversity.[13] They found that MA-exposed children experienced more changes in guardianship, extreme poverty, a reduced executive cognitive function such as attention and accuracy, and higher incidence of anxiety and aggression. Aside from identifying demographic information on MA use, this study highlights the real outcomes of the children affected by MA use not only in their own development but from the surrounding environments in which they are raised. As for the populations affected, Good et al. conducted an extensive chart review like the IDEAL studies and found that most MA mothers that presented were white, unemployed women with less than a high school education.[7] Half of the study's MA-exposed pregnancies resulted in preterm delivery and tended to be high risk due to few (typically < 5) or delayed prenatal visits and domestic abuse (stress), on top of substance abuse. Establishing neurobehavioral and environmental outcomes of MA-exposed children allows researchers to delve deeper into the mechanistic underpinnings of exposure.

The most non-invasive way to determine MA involvement in structure / morphological development is imaging studies. Roussotte et al. used functional magnetic resonance imaging (fMRI) to observe activation differences between MA + alcohol-exposed children, alcohol only, and non-exposed controls.[15] Not only did Roussotte's team observe greater inaccuracies in verbal memory tasks, they also found decreased levels of functional activation in the frontal gyrus, caudate nucleus, and putamen of the MA + alcohol-exposed children during these tasks. Another type of imaging, called diffusion tensor imaging (DTI), records the diffusion of water through brain fibers. DTI can indicate the strength of cross-regional brain connections and changes in microstructural integrity by measuring the strength and direction of water flow. However, only one study by Warton et al. has used DTI to examine the effects of MA exposure.[16] DTI revealed lower efficiency of the connections within the striatum (between left and right caudate nuclei), orbitofrontal cortex, and other limbic structures in MA-exposed children compared to nonexposed controls. These imaging studies suggest that MA exerts is effects primarily on the striatum and other limbic structures, which is consistent with the striatal connectivity alterations seen in DT imaging studies of adult MA users.[17]

Rodent studies give insight to human functions

Keep in mind that the effects of MA seen in human applications are often compounded with other substance usage such as tobacco, alcohol, and marijuana. Due to polysubstance abuse in humans, research on the neurological mechanisms that facilitate the external effects of MA is

best suited for a rodent laboratory, as this eliminates discrepancies in self-reports and other confounding variables such as multiple substances or lack of follow up. To understand the effect of MA at critical developmental periods, Schaefer et al. administered MA or saline vehicle during postnatal days (P) 11-15 and 11-20 to groups of rat pups and measured the resulting hippocampal corticosterone and serotonin levels, as it is known that disruptions in these monoamine balances can cause short- and long-term deficits in cognition.[18] In MA-exposed rats, there were increased levels of corticosterone and decreased serotonin expressed on P16 but changes were mostly attenuated by P30. This effectively identifies the short-term effect of MA use on development.

MA exposure induces long-term alterations in function, structure, and receptor and neurotransmitter expression in different brain regions. Crawford et al. found that dopamine content and dopamine receptor expression were detectably reduced in the rat dorsal striatum 70 to 90 days after their last MA exposure.[19] The number of dendritic spines is reduced in the prefrontal cortex and other limbic areas such as the hippocampus and nucleus accumbens under similar conditions.[20] A lack of dendritic spine densities and dopamine content could explain the decrease in functional activation observed in these regions of an MA-exposed child's brain.[15] However, an increase in gene expression of dopamine D3 receptor in the striatum, carboxylesterase 2 in the hippocampus, and glucocorticoid nuclear receptor in the prefrontal cortex of rats has also been observed.[20] An increase in expression has been hypothesized to be a compensation for deficits in other areas. In addition, MA-exposed rats also demonstrate increased compulsive behavior and motivation for reward, which may speak to the behavioral problems observed in human studies.[21] These results add to the growing evidence that MA exerts its effects primarily on dopaminergic projections, limbic structures, and the prefrontal cortex, which are responsible for a variety of things such as impulse control, locomotor function, and memory.

Conclusions

While a great deal of neonatal drug research has focused on the more acutely impactful drugs such as cocaine and opiates, this literature review sheds light on the negative impact of MA use on the developing brain. Human studies have been able to detail not only who is affected by the growing use of MA, but *how* they are affected in development and by their environment. Not only are the affected children burdened by increased adversity, they are also faced with a potential cognitive disadvantage in comparison to their unexposed peers, as they have an increased prevalence of anxiety and issues with concentration. Rodent studies fill the mechanistic gaps in knowledge left by observations of human behavior and outcomes by confirming MA involvement in limbic and executive control regions.

A diffusion tensor imaging (DTI) study of MA-exposed children to observe microstructural changes has been done once, but I think that these imaging techniques could also be beneficial for use in rodent models as well (Warton et al., 2018). If used in a rodent MA model, DTI and even fMRIs could be directly compared with the physical and genetic changes described in the rodent literature of this review. Microstructural changes in the DTI of rodents could serve to validate findings in human subjects, which would bolster the argument that rodent models are applicable to human findings. The reverse can also be shown if protein kinase A (PKA) levels, an enzyme related to dendritic spine development, are able to be observed in humans. Taken together, the studies covered in this review provide a good starting point for further investigations into the role that MA plays in neurodevelopment and behavioral outcomes, especially with regards to the striatum and prefrontal cortex.

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