Brief Communication

Maternal Opioid Addiction Results in Permanent Memory loss of Off-springs: Are We Aware?

Ashraf I[1], Ashraf S[2], Mohamad N[3], Alam MK[4*]

Addiction during pregnancy is a persistent public health issue that has been associated to sever adverse outcomes. Prenatal opioid exposure is a risk factor for the development of externalizing behaviors and is related with numerous adverse health outcomes. Impaired memory performance in offspring is one of the long-lasting neurobehavioral consequences of prenatal opiate exposure. Opioids are highly addicting, and their prolonged use leads to withdrawal symptoms that can be extremely unpleasant and produce extreme discomfort. All opioids (e.g., heroin, morphine, hydromorphone, oxycodone, codeine, and methadone) causes similar effects by interacting with endogenous (produced by the body itself) opioid (μ, δ, and κ) receptors (that is, specific sites on cells where these substances bind to the cell). Opioid addiction is a chronic disease with great genetic contribution and a large inter-individual variability in therapeutic response. A U.S. multicenter study inspecting the rates of prenatal drug use by meconium analyses and maternal self-report showed that 10.7 percent of 8,527 infants screened were exposed to cocaine or opiates.[1] Though now a days more people abuse prescription pain relievers than illegal opiates, most research on opiates has intricated subjects who are addicted to heroin or receiving opioid agonist therapy.[2] Opioid use earlier to conception or in early pregnancy has been linked with an higher risk for birth defects, including hypoplastic left heart syndrome, one of the most critical heart defects. According to an ongoing, population-based study conducted by the Centers for Disease Control and Prevention (CDC), women receiving opioid analgesic treatment in early pregnancy had a 2- to 3-fold higher risk of delivering infants with conoventricular septal defects, atrioventricular septal defects, hypoplastic left heart syndrome, spina bifida, or gastroschisis.[3] Follow up studies of children prenatally exposed to opiates ,it has been found evidence of delayed general cognitive function at 3 years[4], lower verbal ability, and impaired reading and arithmetic skills.[5] Prenatal opiate exposure has repeatedly been linked with behavioral problems in childhood. One study showed that opiate-exposed children were more likely to have ADHD or other disruptive behavior diagnoses at 10 years of age.[6] Studies of prenatal opiate exposure and infants' early cognitive development have produced mixed results, but there seems to be a pattern linking the exposure to behavioral problems, including increases in ADHD and other disruptive behaviors. The ability to store and recall information is one of the most remarkable capacities of higher organisms. There is a growing body of evidence showing the long lasting neurobehavioral and/or cognitive disturbances due to prenatal opiates exposure. Animal studies have revealed that learning and memory processes can be damaged by prenatal morphine exposure.[7] In the uterus, morphine exposure impairs

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1. Irfan Ashraf, Faculty of Medicine and Health Sciences (FPSK), Universiti Sultan Zainal Abidin (UniSZA), 20400, Kuala Terengganu, Terengganu, Malaysia.
2. Saima Ashraf, BRAIN network Center, School of Health Sciences, Universiti Sains Malaysia, Kelantan, Malaysia
3. Nasir Mohammad, Innovation and Research; FPSK, UniSZA, 20400, Kuala Terengganu, Terengganu, Malaysia.
4. Mohammad Khursheed Alam, School of Dental Sciences, Universiti Sains Malaysia, Kelantan, Malaysia

Corresponds to: Mohammad Khursheed Alam, Senior Lecturer, Orthodontic Unit, School of Dental Sciences, Health Campus, University Sains Malaysia. **E-mail:** dralam@gmail.com, dralam@usm.my

hippocampal long-term potentiation or depression due to reduced expression of NMDAR subunits (NR1, NR2A, and NR2B), postsynaptic density protein 95 and neuronal nitric oxide synthase, reduced phosphorylation of CREBSerine-133, and also decreased GABAergic inhibition. Prenatal morphine exposure delays the neural tube closure and increases the rate of neuroblast apoptosis in developing neural system.[8] This prenatal imbalanced apoptosis may persist even after birth, as in a recent study the memory deficits resulted from prenatal heroin exposure is attributed to the increased neuronal apoptosis in the hippocampus of young offspring.[9] Given that the hippocampus sub serves a significant role in learning and memory processes.[7]

In a study done by Nasiraei-Moghadam et al 2013, they exposed that prenatal morphine exposure has long-term effects on passive avoidance memory retention, hippocampus neuronal viability, and expression of proteins implicated in synaptic plasticity, and differentially impairs adolescent and adult male and female offspring. According to their results, females were more predisposed than males to be affected by prenatal morphine in the passive avoidance retention task, regardless of the duration of morphine exposure. In addition, morphine-induced deficits persisted in female offspring even after puberty. Prenatal morphine exposure impairs symmetrical maze learning task and radial arm maze memory performance in a sex-dependent manner, as adult male offspring show more sensitivity to be affected by prenatal morphine exposure than adult females.

Studies of learning and memory in animal models have recognized a number of gene products that are necessary for these processes. One of them is brain-derived neurotrophic factor (BDNF). Neurotrophins are essential for the development of the nervous system of vertebrates. Among neurotrophins, BDNF, and its key receptor TrkB, has the most abundant and widespread expression in the developing and adult mammalian brain. Similarly, the action of this neurotrophin in the adult CNS is now the most comprehensively studied, perhaps because it has been shown to have a vital role in long-term potentiation (LTP), a form of synaptic plasticity which is still broadly considered a cellular model of long-term memory (LTM) Formation. The neurotrophin family is involved in neural plasticity, learning, memory and behavior and deregulated neural plasticity may

Table 1. Effects of maternal opioid addiction on pregnancy outcomes

Author	Findings
Nasiraei-Moghadam et al[7]. 2013	Damaged memory and learning process
Nasiraei-Moghadam et al[8]. 2010	delays the neural tube closure and increases the rate of neuroblast apoptosis in developing neural system
Yang et al[9]. 2003	Increased neuronal apoptosis in the hippocampus of young offspring
Wilson et al[4]. 1979	delayed general cognitive function at 3 years
Ornoy et al[5]. 2001	lower verbal ability, and impaired reading and arithmetic skills
Centers for Disease Control and Prevention (CDC) report [1]	women receiving opioid analgesic treatment in early pregnancy had a 2- to 3-fold higher risk of delivering infants with conoventricular septal defects, atrioventricular septal defects, hypoplastic left heart syndrome, spina bifida, or gastroschisis
Hans[6], 1989	Likely to have ADHD or other disruptive behavior diagnoses at 10 years of age
Cunha et al[10]. 2010	The addition of BDNF restores learning after endogenous depletion of BDNF

underlie the pathophysiology of drug addiction. BDNF has appeared as an important mediator of synaptic plasticity. It not only plays a part in LTP and LTD but it is perhaps the key instructor for plasticity-related processes underlying LTM. This is principally exemplified by "rescue" studies where the addition of BDNF restores learning after endogenous depletion of BDNF.[10]

Mice with a targeted gene deletion of brain-derived neurotrophic factor (BDNF) showed a wide-based gait. Consistent with this behavioral evidence of cerebellar dysfunction, there is augmented death of granule cells, stunted growth of Purkinje cell dendrites, impaired formation of horizontal layers, and defects in the rostral–caudal foliation pattern. These deformities are accompanied by decreased Trk activation in granule and Purkinje cells of mutant animals, representing that both cell types are direct targets for BDNF. This data suggest that BDNF acts as an anterograde or an autocrine–paracrine factor to regulate survival and morphologic differentiation of developing CNS neurons thus affects neural patterning.[11]

BDNF precursor protein was reduced in prenatal morphine-exposed juvenile female rats. Given that hippocampal BDNF is essential for both short- and long-term memory formation of inhibitory avoidance6. Memory dysfunctions due to prenatal morphine exposure could be partly attributed to reduced BDNF levels. In another study, it is also revealed that prenatal opiate exposure decreases the levels of BDNF precursor in hippocampus, and this reduction is accompanied with impaired memory performance in adult male rats.[7]

Maternal addiction not only places the woman at increased risk for medical and obstetrical complications but also the fetus has to face the catastrophic effects throughout his life.

Conflict of Interest: None Declared

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