Generational Effects of Opioid Exposure

Subjects: Tropical Medicine

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The inheritance of substance abuse, including opioid abuse, may be influenced by genetic and non-genetic factors related to the environment, such as stress and socioeconomic status. These non-genetic influences on the heritability of a trait can be attributed to epigenetics. Epigenetic inheritance can result from modifications passed down from the mother, father, or both, resulting in either maternal, paternal, or parental epigenetic inheritance, respectively. These epigenetic modifications can be passed to the offspring to result in multigenerational, intergenerational, or transgenerational inheritance. Human and animal models of opioid exposure have shown generational effects that result in molecular, developmental, and behavioral alterations in future generations.

Keywords: Keywords: opioids ; morphine ; heroin ; oxycodone ; multigenerational ; intergenerational ; transgenerational ; humans ; animals

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The ongoing opioid epidemic in the United States and worldwide is characterized by an increase in use of licit and illicit opioid substances, such as prescription opioids, illicit heroin, and illicitly-produced fentanyl. While steps have been taken by the FDA to limit opioid abuse and misuse, the potential for addiction remains an issue, especially when individuals turn to cheaper, illicit opiates as an alternative to prescription opioids [1]. Further, opioids are commonly prescribed to postpartum women, often in abundance [2][3], making pregnant women a particularly vulnerable group in the opioid epidemic. Additionally, mounting evidence suggests that substance use disorders, such as opioid abuse, run in families [4][5]; twin, adoption, and sibling studies implicate genetic factors are involved in the heritability of substance abuse [6]. Several human genome-wide association studies have been done to identify loci and genes associated with addiction and substance use disorders [5][7][8], revealing heritability estimates of substance use between 0.39 and 0.72 [7]. However, the inheritance of substance abuse cannot be explained entirely through genetic mechanisms alone. Environmental factors, such as stress and socioeconomic status, also shape an individual's susceptibility to addiction [9].

Generational Inheritance

These non-genetic influences on the heritability of a trait can be attributed to epigenetics. Epigenetics is the alteration of gene expression without changes to DNA sequence [10][11], which can be accomplished through acetylation or methylation of the histone complexes [12]. Epigenetic inheritance can result from modifications passed down from the mother, father, or both, resulting in either maternal, paternal, or parental epigenetic inheritance, respectively. Because these epigenetic modifications can be passed to the offspring, it is important to define the type of generational inheritance: multigenerational, intergenerational, or transgenerational [13].

Skinner has defined transgenerational inheritance as "germ-line-mediated inheritance of epigenetic information between generations in the absence of direct environmental influences that lead to phenotypic variation," meaning a true transgenerational study must include at least one generation that receives no direct exposure to the stimulus [14]. While the definition of transgenerational inheritance is fairly straightforward, defining inter- and multi-generational inheritance is slightly more difficult. Vassoler et al. provide the simplest definitions for inter- and multi-generational inheritance [13]. If the F0 drug use occurs in males or in females prior to pregnancy, the germ cells, which will become the F1 generation, are exposed to the drug. Because both the F0 and the F1 generations are directly exposed to the drug, their inheritance pattern is considered intergenerational. In this scenario, the F2 generation would be the first generation not exposed to the drug, resulting in transgenerational inheritance. Alternatively, if the F0 female is exposed to the drug during pregnancy or postpartum, the somatic and germ cells of the F1 offspring receive direct exposure to the drug in utero or postpartum via the breastmilk [12]. Since the F1 germ cells are exposed to the drug, and the F2 offspring originate from those germ cells, the first generation without direct exposure to the drug is F3. In these cases, a study spanning from F0 to F3 would be considered transgenerational, as F3 is the first generation without direct exposure; a study spanning from F0 to F2 would be considered multigenerational.

Hanson et al. have outlined the definition of multigenerational inheritance as "coincident direct exposure of multiple generations to an environmental factor promoting alterations in the multiple generations exposed" [15]. Therefore, in the

scenario of drug exposure during F0 pregnancy, the relationship among F0, F1, and F2 would be multigenerational, as the effects of direct exposure to the drug span more than two generations. The paired relationships between F0–F1 and F1–F2, however, would be intergenerational, as these pairs span only two generations post-direct drug exposure. A depiction of multi-, inter-, and trans-generational types of inheritance are shown in **Figure 1**.

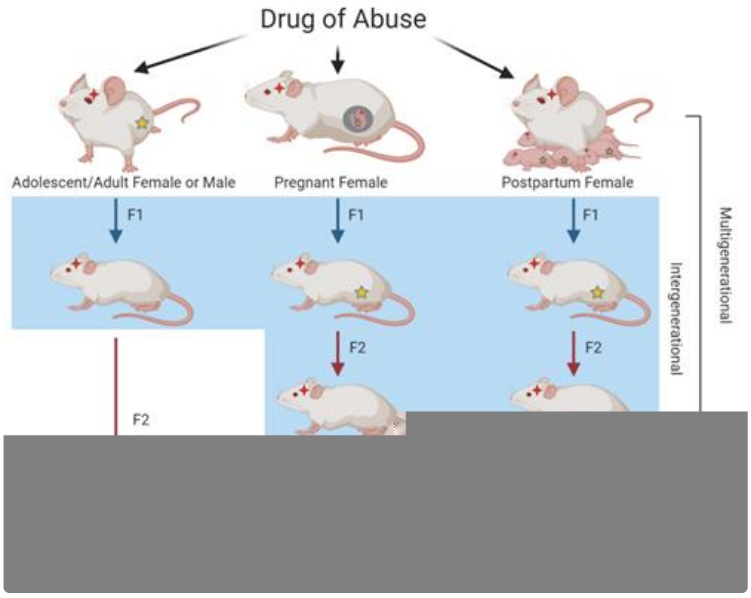

Figure 1. Illustration of multi-, inter-, and trans-generational relationships resulting from parental drug exposure. When F0 males or females are exposed to drugs of abuse in adolescence or adulthood, the germ cells that give rise to the F1 generation are directly exposed, resulting in intergenerational transmission. Because the germ cells of the F1 generation were not directly exposed, the F2 generation represents transgenerational transmission. When F0 pregnant or postpartum breastfeeding females are exposed, the F1 generation and their germ cells that will give rise to the F2 generation are also directly exposed, resulting in intergenerational transmission. For both of these scenarios, the F3 generation is the first without direct drug exposure and therefore represents transgenerational transmission. As F0–F2 generations have direct drug exposure in the case of pregnant or postpartum females, the relationship among the three generations represents multigenerational transmission. Red stars represent direct exposure to that particular generation while yellow stars represent direct exposure to the germ cells.

With regard to generational studies and opioid exposure, studies involving in utero exposure to opioids are particularly critical, as these may result in neonatal opioid withdrawal syndrome (NOWS) or neonatal abstinence syndrome (NAS). Neonates with NOWS/NAS exhibit high-pitched cries, tremors, difficulty feeding, hypertonia, and breathing issues [16]. In the context of in utero opioid exposure and NOWS/NAS, the fetal origins of adult disease hypothesis, first posited by Dr. David Barker in 1995 [17], is particularly interesting. This hypothesis states that risk factors from intrauterine environmental exposures affect fetal development during sensitive periods, and increase the risk of specific diseases in adult life [18]. Indeed, prenatal exposure to opioids has been associated with smaller head size, lighter birthweights, and shorter body lengths in neonates [19][20][21][22][23][24]. Moreover, not only do young adults exposed to heroin prenatally exhibit cognitive and motor function deficits [25][26], but they may also have an 8-fold increased risk of depression, a 3-fold increased risk of attention disorders, and a 16-fold increased risk of substance use disorders [27]. As substance use disorder is considered a disease, it is critical to understand how the generational effects of opioid exposure manifest in not only newborns, but adults as well.

This review aims to discuss the generational effects of opioid exposure in animal and human studies. The following sections will provide a brief overview of opioids and discuss the molecular and behavioral changes reported in exposed generations and, where applicable, whether these changes are present long-term. As the opioid epidemic continues, understanding the generational impacts and long-term effects of opioid exposure is paramount.

Opioids

Opiate analgesics have a long history of clinical use in the treatment of chronic pain. First derived from opium in 1803 [28], morphine became widely used with the technological innovation of the perfected hypodermic syringe in 1853, which allowed for faster delivery of morphine into the blood or tissue. The American Civil War (1861–1865), the Prussian–Austrian War (1866), and the Franco–Prussian War (1870) also rapidly increased the use of morphine for the reduction of pain and relief from dysentery, often leading to a dependence later deemed “soldier’s disease” or the “army disease” [29].

In England, morphine was first recommended for treatment of cancer pain in the 1950s [30]. Taken orally or by injection, morphine is still widely used today for acute and chronic pain management. Unfortunately, opioids are also used illicitly and often taken in excess, affecting the behavior of the user [31].

Whether used licitly or illicitly, opioids activate three types of receptors (mu, MOR; delta, DOR; kappa, KOR) in the dopaminergic system. The nucleus accumbens (NAc) is largely affected and undergoes changes in density of the dendritic spines [31], effectively altering the plasticity of the dendritic spines during nervous system development. This neural plasticity is critical in the development of addiction and other ingrained behaviors. The increased abuse of prescription and non-prescription opioids has resulted in a severe public health crisis throughout large swaths of America [32][33][34]. In 2017, over two-thirds of drug-overdose deaths resulted from opioid abuse [35], and opioid overdose-attributed deaths have tripled since the turn of the new millennium [36]. The main opioids discussed in this review are morphine, heroin, and oxycodone.

Morphine

Morphine is a potent analgesic primarily used in hospitals to combat severe pain. While morphine may be effective for pain relief, there are potential adverse side effects such as tolerance and addiction as well as molecular alterations [37]. Morphine's powerful analgesic effects stem from its role as an opioid receptor agonist. By binding to MOR and KOR, morphine blocks the transmission of nociceptive signals, signals pain-modulating neurons in the spinal cord, and inhibits primary afferent nociceptors to the dorsal horn sensory projection cells [38]. Morphine also activates the reward pathway by binding to receptors in the ventral tegmental area (VTA) and NAc, leading to an influx of dopamine in the synapse [39].

Heroin

The result of a chemical modification to morphine, heroin is about three times as potent as its parent drug [29]. Unlike morphine, which can be prescribed, heroin is an illicit substance. Like other opioids, heroin acts agonistically to the three opioid receptors. A particular danger in heroin use is that heroin often contains additives that may clog blood vessels leading to the lungs, liver, kidneys, or brain, causing permanent damage. Needle sharing and impaired judgment resulting from heroin use can also increase the risk of contracting infectious diseases such as HIV and hepatitis [40].

Oxycodone

Structurally similar to morphine, oxycodone has been established as a potent and widely abused prescription opioid. Designed for pain management, oxycodone operates primarily as a full agonist to MOR [41]. The binding of oxycodone to MOR subsequently inhibits neurotransmitter release by decreasing cAMP production [41]. Importantly, oral doses of extended release oxycodone are thought to be twice as potent as a similar dose of morphine [42], contributing to its popularity and abuse.

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