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Minireview

Behavioral effects of perinatal opioid exposure

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ABSTRACT

Opioids are among the world's oldest known drugs used mostly for pain relief, but recreational use is also widespread. A particularly important problem is opioid exposure in females, as their offspring can also be affected. Adverse intrauterine and postnatal environments can affect offspring development and may lead to various disabilities later in life. It is clear that repetitive painful experiences, such as randomly occurring invasive procedures during neonatal intensive care, can permanently alter neuronal and synaptic organization and therefore later behavior. At the same time, analgesic drugs can also be harmful, inducing neuronal apoptosis or withdrawal symptoms in the neonate and behavioral alterations in adulthood. Hence, risk–benefit ratios should be taken into consideration when pain relief is required during pregnancy or in neonates.

Recreational use of opioids can also alter many aspects of life. Intrauterine opioid exposure has many toxic effects, inducing poor pregnancy outcomes due to underdevelopment, but it is believed that later negative consequences are more related to environmental factors such as a chaotic lifestyle and inadequate prenatal care. One of the crucial components is maternal care, which changes profoundly in addicted mothers. In substance-dependent mothers, pre- and postnatal care has special importance, and controlled treatment with a synthetic opioid (e.g., methadone) could be beneficial.

We aimed to summarize and compare human and rodent data, as it is important to close the gap between scientific knowledge and societal policies. Special emphasis is given to gender differences in the sensitivity of offspring to perinatal opioid exposure.

Contents

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Introduction

Opiates are drugs derived from opium (e.g., morphine, heroin, codeine), a powdered dried exudate of the fruit capsule (poppy) of the plant *Papaver somniferum*, that act on opioid receptors in our body. Opioids are among the world's oldest known drugs; archeological evidence and fossilized poppy seeds suggest that Neanderthals may have used these drugs over thirty thousand years ago (Rosenfeld and Loose, 2007). The drugs' main effect is to relieve pain, so they are powerful analgesics. Furthermore, opioids are well known for their ability to produce euphoria, motivating certain individuals to engage in recreational use.

The potential danger of most opioids is that prolonged use results in physical and psychological dependence (Kaltenbach, 1996). According to a study published in *The Lancet* (Kapp, 2003), heroin is the most dangerous drug among those studied based on its physical harm to the user, addictive potential and overall negative impact on society. In 2010, there were reportedly as many as 2.4 million people in the United States (US) with an opioid problem (Rockville, 2011). However, the majority of opioids used in the US originate from a legal doctor's prescription written to treat pain.

A particularly important problem is the use of opioid drugs (both painkillers and "street drugs") in females, as these drugs may also influence offspring. Similar to many abused drugs, morphine can cross the placenta and blood–brain barrier and even exudes into the breast milk. Opioid receptors are present in several areas of the brain, and multiple mechanisms can be affected by opiate exposure (Yanai et al., 2003). Based on data averaged across 2010 and 2011 in the US, among pregnant women (15–44 years old), 5% were current illicit drug users (Rockville, 2012). Rats are used extensively to study the developmental effects of opiates because many of their responses to drugs resemble those of humans (Bashore et al., 1981). However, there is a gap between rodent-based scientific knowledge and societal policies (Thompson et al., 2009).

We aimed to review the effect of opioid treatment/use on offspring, comparing human and rodent studies, with the goal of identifying the gaps between the two study types. We follow a "chronological" order, from preconceptional effects to intrauterine treatments and treatments during labor to the early and late consequences of postnatal administration, with special emphasis on possible gender differences.

Preconceptional use

Human studies

It is known that preconceptional effects can profoundly alter later pregnancy and the fetus (Twigt et al., 2012). Despite this fact, in humans, the pregnancy rate is not influenced by injection drug (such as heroin) use (Weber et al., 2003). We must mention, however, that low uptake of reliable contraception can confound the results.

Animal studies

Appropriate usage of morphine can be beneficial in enhancing the pregnancy rate, based on a study using embryo transfer in rats (Smith et al., 2004). In rodents, a premating morphine exposure regimen (prior to pregnancy) had no effect on maternal behavior (Yim et al., 2006; Johnson et al., 2011) but induced long-term effects in offspring. In line with this finding, the female offspring of dams exposed to morphine during puberty displayed increased anxiety-like behavior both in the elevated plus-maze (EPM) and in a novel environment, possibly due to altered prolactin regulation (Byrnes, 2005a). The male offspring of females exposed to morphine during adolescence showed alteration in their early social playing behavior (Johnson et al., 2011). Thus, there is a transgenerational effect of opioid exposure, with gender-specific alterations (Slamberova et al., 2005).

Prenatal exposure

Human studies

Among the opioids, heroin, methadone and buprenorphine (the last two are synthetic opioids used as anti-addictive maintenance preparations) are the forms most commonly used by pregnant women (Bhuvaneswar et al., 2008). Opioids undergo rapid transplacental passage (less than 60 min), and maternal and fetal withdrawal is likely to begin 6–48 h after the last use (Bhuvaneswar et al., 2008).

Pregnancy complications, including premature rupture of the membranes, meconium-stained liquor and fetal distress, are more common in women who misuse drugs (Johnson et al., 2003). The incidence of stillbirths and neonatal mortality in addicts is 2–4 times higher than that in the general population (Lam et al., 1992). Moreover, sudden infant death syndrome is seven times more frequent in the children of addicts than in the normal population. The principal causes of infant death are prematurity and growth retardation (Bashore et al., 1981). In a Chinese population, babies born to drug-addicted mothers were on average 629 g lighter at birth, 5 cm smaller in head circumference and 7 cm shorter in body length (Lam et al., 1992). Adverse consequences are associated with many incremental social, psychosocial and contextual factors, such as a chaotic lifestyle, incomplete nutrition, intrauterine infections and inadequate prenatal care (Schempf, 2007). In fact, 75% of pregnant heroin addicts do not receive any prenatal care (Bashore et al., 1981).

Methadone treatment during pregnancy offers overwhelming advantages compared with the less acceptable option of medical detoxification or the unacceptably dangerous option of leaving heroin-addicted women dependent on street drugs (Kandall et al., 1999). The Maternal Opioid Treatment: Human Experimental Research (MOTHER) project found both methadone and buprenorphine to be important parts of a comprehensive treatment approach (Jones et al., 2012a, 2012b). Many studies examining neonatal outcomes among pregnant heroin users treated with methadone have reported improvements in birth weight (Strauss et al., 1974; Kandall et al., 1975). Therefore, methadone treatment has become the 'gold standard' for management of the pregnant heroin user. However, subsequent studies have suggested that heroin use while receiving methadone may counteract the birth weight advantage gained from methadone alone (Hulse et al., 1997), but this phenomenon may be connected to the chaotic and high-risk lifestyle of users as well (Hulse et al., 1998). Further studies are required to identify important factors related to drug use (e.g., social circumstances, poor nutrition, stress, infections). Influencing these factors will be beneficial to improving neonatal outcomes (Schempf, 2007).

Neonatal abstinence syndrome (NAS), or withdrawal symptoms, occur in 55–94% of neonates exposed to opiates in utero, without a significant difference between male and female infants (Holbrook and Kaltenbach, 2010). Commonly observed symptoms include irritability, high-pitched crying, tremors, hypertonicity, vomiting, diarrhea and tachypnea (Johnson et al., 2003). The onset of signs attributable to neonatal withdrawal from heroin often begins within 24 h of birth,