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Minireview

# Behavioral effects of perinatal opioid exposure

Anna Fodor [a,b], Júlia Tímár [c], Dóra Zelena [a,*]

[a] Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary
[b] János Szentágothai School of Neurosciences, Semmelweis University, Budapest, Hungary
[c] Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary

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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**



* Corresponding author at: Institute of Experimental Medicine, Hungarian Academy of Sciences, 1083 Budapest, Szigony 43, Hungary. Tel.: +36 1 210 9400; fax: +36 1 210 9951.
*E-mail address:* zelena.dora@koki.mta.hu (D. Zelena).

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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,

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whereas withdrawal from methadone can be delayed. Infants scoring over a certain numerical threshold on abstinence tests are treated with medication (Jansson et al., 2009). The goal of medication therapy is the stabilization of more severely symptomatic infants, allowing them to eat, sleep, gain weight and interact with caregivers. However, the pharmacologic management of NAS remains a challenge. Opioid agonist medications are thought to be the most effective agents in the treatment of neonatal neurobehavioral problems related to in utero opioid exposure. In 2005, the Cochrane Review failed to identify a specific opioid as optimal for the treatment of infants undergoing opioid withdrawal (Osborn et al., 2005). A later review, published in 2011, suggested oral morphine solutions as the mainstay of NAS therapy (Bio et al., 2011).

Later consequences of in utero opioid exposure have also been described in humans. Inattention, hyperactivity, impulsivity and aggression, the major diagnostic criteria of attention deficit hyperactivity disorder (ADHD), are known to persist into adulthood in children born to heroin-dependent mothers or to mothers using methadone during pregnancy (Ornoy et al., 1996). One of the major factors affecting the development of these children is the environment in which they are raised (Ornoy et al., 1996, 2001; Weisglas-Kuperus et al., 1993). Among children born to heroin-dependent mothers raised by adoptive families, hyperactivity was found in a significantly lower percentage than among children exposed to heroin in utero and raised by their biological families.

Nevertheless, the effects of prenatal exposure to drugs on brain development are complex and are modulated by the timing, dose and route of drug exposure (Thompson et al., 2009). Therefore, it is difficult to assess these effects in clinical cohorts, which are beset with problems such as difficulties in documenting use patterns (Jones et al., 2012a). Thus, animal studies are required.

*Animal studies*

The immature brain seems to be particularly vulnerable to the actions of opiates (Bashore et al., 1981). Opiates appear to selectively accumulate in the nervous tissues of offspring because of increased permeability of the blood–brain barrier and may affect the development of the central nervous system (CNS) and cause a variety of delays in ontogeny (Peters et al., 1972; Shah and Donald, 1979). Similar to observations in humans, the administration of opiates during fetal development may result in increased intrauterine death, thereby decreasing litter size, in rodents (Fujinaga and Mazze, 1988). Although no teratogenic effects were observed with the chronic administration of morphine in one study, the number of stillbirths and infant mortality increased, and the body growth of the offspring of drug-exposed female rats was stunted (Zagon and McLaughlin, 1977). Fetal exposure to opiates may adversely affect the migration and survival of neurons in rat embryos, thereby leading to an overall inhibition of brain growth and development during this critical period of CNS development (Vathy, 1995; Walhovd et al., 2009). Exposure to opiates prenatally can alter opioid receptor density and distribution. This phenomenon can in turn affect the development of neural connections by delaying or accelerating neural outgrowth. Indeed, heroin exposure in pregnant mice decreased dendrite length and branch numbers in pyramidal neurons in the somatosensory cortex of offspring (Lu et al., 2012).

Later consequences of intrauterine drug exposure have been extensively studied in rodents (Table 1). Our own data also support long-term consequences in the offspring of morphine-exposed mothers (from the day of mating until weaning) (Klausz et al., 2011). The persisting somatic changes (Fig. 1) included body and adrenal gland weight decreases, which were a sign of disturbed stress-axis regulation, and altered blood glucose levels (Fig. 3D) (Castellano and Ammassari-Teule, 1984). Changes in motor development and analgesia have also been described (Castellano and Ammassari-Teule, 1984; Eriksson and Ronnback, 1989; Gagin et al., 1996; Robinson and Wallace, 2001). Adult mice that underwent prenatal heroin exposure showed certain signs of impaired short-term spatial memory (Lu et al., 2012). Prenatal morphine exposure may result in enhanced activity and/or sensitivity of the endogenous opiate system, thereby placing the organism at higher risk of opiate drug addiction (Gagin et al., 1997a; Timar et al., 2010; Sobor et al., 2010). Indeed, Ramsey et al. found that prenatal morphine exposure enhanced the reinforcing effects of heroin and cocaine, as measured by self-administration (Ramsey et al., 1993). Prenatal morphine treatment also has an age-dependent effect on seizure susceptibility, which is highly influenced by gonadal hormones, with males being more vulnerable than females to morphine-induced insults during prenatal brain development (Vathy, 2001; Vathy et al., 1998; Slamberova and Vathy, 2000; Schindler et al., 2000; Velisek et al., 1998). As a possible explanation, mu-opioid receptors in seizure-controlling brain structures are sex-specifically altered by prenatal morphine exposure in adult progeny (Slamberova et al., 2002).

There is gender dimorphism in the rodent brain (Vathy, 1995), as prenatal morphine exposure reduces female sexual behavior but does

**Table 1**
A summary of behavioral consequences of prenatal opioid exposure in rodent models.

| Behavioral alteration | Tests | Difference | Reference |
|---|---|---|---|
| Motor coordination | Postnatal reflexes | Slightly reduced | Castellano and Ammassari-Teule (1984) |
| | Spontaneous activity | Reduced on PND1, no difference in adult | Castellano and Ammassari-Teule (1984) |
| Anxiety | Novel environment | Anxiogenic | Byrnes (2005a), Timar et al. (2010) |
| | Open field | No alteration | Hamilton et al. (2005) |
| | Elevated plus maze | Anxiogenic | Byrnes (2005a), Klausz et al. (2011) |
| | Startle response | Enhanced in male, no change in female | Hamilton et al. (2005) |
| Depression | Forced swim test | Depression-like | McPherson et al. (2007), Klausz et al. (2011) |
| | Saccharin preference | Enhanced | Gagin et al. (1996) |
| Learning | Symmetrical maze | Faster learning in males but not females | Slamberova et al. (2001a) |
| | Passive avoidance | Impaired | McPherson et al. (2007) |
| Memory | Eight-arm radial maze | Memory decline mostly in females | Slamberova et al. (2001a) |
| Drug sensitivity | Active and passive avoidance | Enhanced | Castellano and Ammassari-Teule (1984) |
| | Pain | Reduced antinociceptive morphine effect | Timar et al. (2010) |
| Analgesia | Hot plate | Enhanced sensitivity to morphine | Eriksson and Ronnback (1989), Gagin et al. (1996) |
| | Tail-flick | Reduced tolerance to antinociceptive effect of morphine | Gagin et al. (1996), Robinson and Wallace (2001), Sobor et al. (2010), Timar et al. (2010) |
| Sexual behavior | | Inhibition in female, no alteration in male | Vathy et al. (1983, 1985, 1999), Gagin et al. (1997b) |
| Drug seeking | Conditioned place preference | Enhanced | Timar et al. (2010), Sobor et al. (2011) |
| Maternal behavior | Spontaneous | Decreased | Moura et al. (2010), Sobor et al. (2010, 2011) |
| | Vs. insect hunting | Maternal care decreased | Cruz Ade et al. (2010) |

The different studies used different treatment protocols. It is obvious, that many alterations can be found after perinatal opioid exposure, however, most of the changes are mild and cannot be detected in both sexes. PND — postnatal day.

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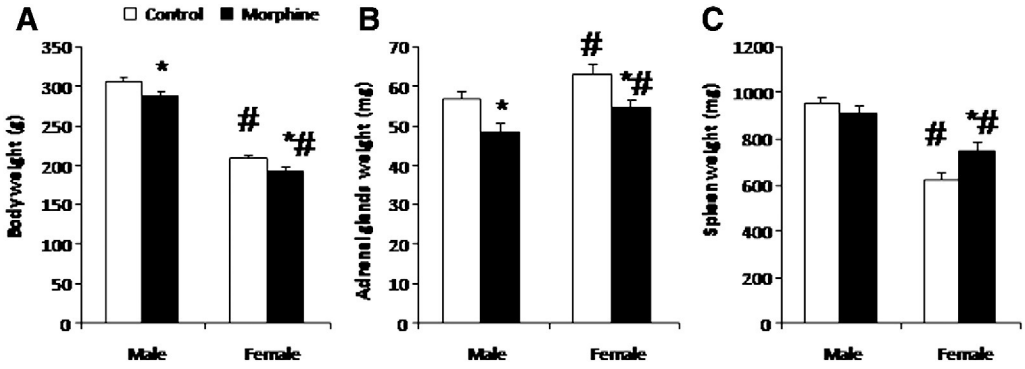


**Fig. 1.** Effects of maternal morphine exposure (from the day of mating until weaning, 10 mg/ml/kg subcutaneously) on body weight (A), the adrenal glands (B) and spleen weight (C) in adult male and female offspring. For method details, see Klausz et al. (2011). N = 10–14. (A) Body weight (g) was smaller in female rats ($p < 0.05$), and morphine treatment significantly reduced this parameter for a prolonged period ($p < 0.05$). (B) The weight of both adrenal glands was higher in females ($p < 0.01$), with a reduction in maternally morphine-treated animals ($p < 0.01$). (C) The weight of the spleen showed an interaction between gender and treatment ($p < 0.05$), with a lower weight in females and a high value in females among morphine-treated animals. *$p < 0.05$ vs. control treatment; #$p < 0.05$ vs. male.

not have a profound effect on males (Vathy et al., 1985). Adult sexual behavior in female rats is both defeminized and masculinized (Vathy, 1999; Gagin et al., 1997b). The inhibition of female sexual behavior (Vathy et al., 1983) is contrasted by enhanced social play during their juvenile age, most likely due to an influence on motivational and reward systems (Niesink et al., 1996). Our results showed similar dimorphism. The weight of the spleen, reflecting immune function, changed in the opposite manner in males and females (Fig. 1C). As susceptibility to mental illnesses is most likely to change (Fumagalli et al., 2007; Maccari et al., 2003), we studied mood-relevant behaviors. This examination of anxiety- and depression-like behavior revealed a significant gender–treatment interaction (Fig. 2). In our case, male offspring were more vulnerable to the anxiogenic and depressogenic effects of intrauterine and postnatal morphine treatment than were females subjected to the EPM and the forced swim test (FST) (Klausz et al., 2011). Similarly, Hamilton and coworkers reported an elevated startle response in the male, but not female, offspring of morphine-treated mothers (Hamilton et al., 2005). Additionally, Slamberova et al.

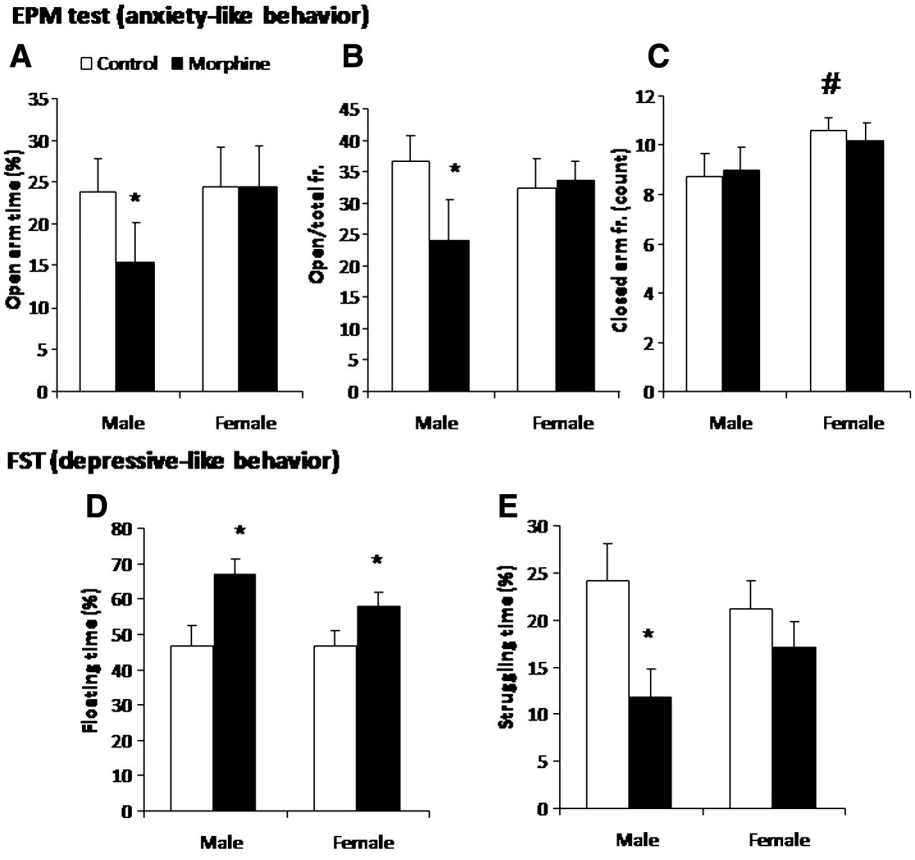


**Fig. 2.** Effects of maternal morphine exposure (from the day of mating until weaning, 10 mg/ml/kg subcutaneously) on elevated plus-maze (EPM) (% of open arm time (A), number of open/total entries (B) and number of closed arm entries (C)) and forced swim test (FST) (% of floating time (D) and time spent in struggling (E)) performance in adult male and female offspring. For the details of the method, see Klausz et al. (2011). N = 12. Anxiety-like behavior was measured in the EPM for 5 min (A–C). Female rats were more active, as suggested by enhanced closed arm entries (C; $p = 0.05$), but morphine pretreatment did not have a similar effect. Treated male rats had an anxiogenic phenotype, whereas pretreatment was ineffective in females (A, B). Depressive-like behavior was tested in the FST (D, E). As a sign of a more depressive-like phenotype, the time spent floating was enhanced in morphine-treated animals (D; $p < 0.05$). There was an interaction between gender and treatment in the case of struggling behavior, as the male rats were more vulnerable (E; $p = 0.05$). *$p < 0.05$ vs. control treatment; #$p < 0.05$ vs. male.

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demonstrated that prenatal morphine exposure differentially altered the performance of adult male and female rats on tasks requiring learning and spatial memory (Slamberova et al., 2001a). Another group reported disturbance in a passive avoidance retention task in females after intrauterine morphine treatment (Degos et al., 2012). We found a significant gender–treatment interaction in the case of stressor-induced blood glucose elevation as well (Fig. 3D).

Dysregulation of the stress axis, and especially alteration in glucocorticoid levels, is a core feature of mood disorders (Joels, 2011). Therefore, it is important to note that prenatal opiate exposure followed by postnatal withdrawal diminished the stress axis response to immunological and social stressors in neonatal rats, whereas in adulthood, an exaggerated response was detected (Hamilton et al., 2005). The adrenocorticotropin (ACTH, the hypophyseal component of the stress response) and corticosterone (a rodent glucocorticoid in the adrenal cortex) responses are dissociated (Rimanoczy et al., 2003; Slamberova et al., 2004). Although there were no differences in basal levels between control animals and intra- and postnatal morphine-treated animals, stressor-induced ACTH elevations were smaller in the opioid-exposed groups. In addition to glucocorticoid regulation, ACTH has many different effects (Zelena and Makara, 2012). Nevertheless, as the end hormones of the axis are glucocorticoids, we are concentrating on these molecules. In our study, resting glucocorticoid levels were elevated in the adult male offspring of morphine-treated dams (among females, the higher basal levels of untreated animals masked any elevation), suggesting chronic stress-like changes (Fig. 3A). FST-induced changes were smaller in morphine-treated groups of both genders (Fig. 3B). The disturbed stress axis suggested damaged adaptive capability (Klausz et al., 2011). Accordingly, we found smaller stress-related organs (Fig. 1B), hypoactivity of the stress axis (Fig. 3B) and enhanced depression-like behavior during the FST (Fig. 2D, E), and males were at greater risk than females were.

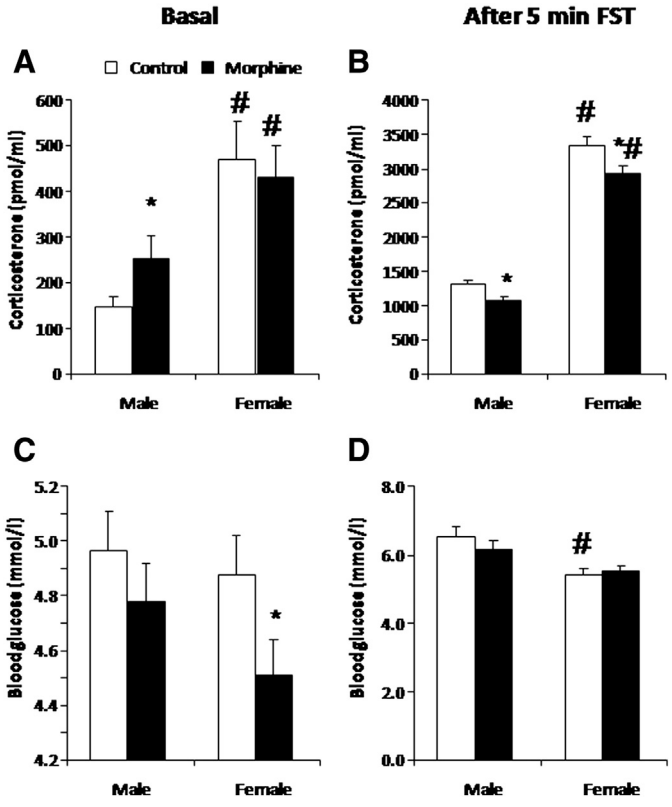


**Fig. 3.** Effects of maternal morphine exposure (from the day of mating until weaning, 10 mg/ml/kg subcutaneously) on serum corticosterone and blood glucose changes: (A, C) basal values and (B, D) after acute stress (5 min FST) in adult male and female offspring. For the details of the method, see Klausz et al. (2011). N = 12. (A) Under basal conditions, female rats had higher corticosterone levels ($p < 0.01$), and morphine pretreatment was able to induce a further increase only in males. (B) At the end of a 5 min challenge, females showed much higher levels ($p < 0.01$). However, maternal morphine treatment diminished the elevation in both genders ($p < 0.01$). (C) Resting blood glucose levels were lower in morphine-treated animals ($p = 0.05$), with more severe changes in females. (D) Stressor exposure induced a smaller increase in females ($p < 0.01$).*$p < 0.05$ vs. control treatment; #$p < 0.05$ vs. male.

*Maternal behavior in animals*

Based on human studies (Ornoy et al., 1996), we cannot rule out the possibility that the above-mentioned late consequences were an indirect result of morphine-induced alterations in maternal physiology and/or behavior. Although premating morphine treatment had no effect (see earlier), treatment during lactation can profoundly influence the mother's behavior. It is known that inadequate maternal care results in altered behavioral and endocrine responses to stress in offspring (Levine, 2005; Weaver et al., 2004).

Plasma and brain levels of endogenous opioids increase over the course of pregnancy, peak during parturition and then decline to pre-pregnancy levels during lactation (Petraglia et al., 1985; Wardlaw and Frantz, 1983). These changes in endogenous opioids are consistent with "pregnancy-mediated analgesia", an elevation in the pain threshold (hypoalgesia) during labor and delivery (Gintzler, 1980). Additionally, systemically administered exogenous opiates inhibit maternal behavior in lactating dams (Sobor et al., 2010; Bridges and Grimm, 1982; Slamberova et al., 2001b). Non-sedative doses of morphine disrupt (e.g., increase the latency to retrieve pups) and naloxone restores maternal responsiveness in female rats (Bridges and Grimm, 1982; Haney and Miczek, 1989). During prolonged administration, sensitization also occurs, meaning that maternal behavior may be inhibited by low doses of morphine (e.g., 3 mg/kg) that are otherwise ineffective at inducing such inhibition in control lactating rats (in which at least 5 mg/kg is needed) (Sobor et al., 2010; Miranda-Paiva et al., 2001; Cruz Ade et al., 2010). Moreover, the rewarding potential of morphine increases in treated dams, measured on conditioned place preference (Sobor et al., 2011). Not only is spontaneous maternal care reduced but behavioral selection between pup care and insect hunting also shifted to the latter direction (Cruz Ade et al., 2010). Late pregnancy was particularly sensitive in terms of morphine's effects on maternal behavior (Yim et al., 2006).

Vathy et al. studied the later consequences of disrupted maternal care by morphine-treated mothers for offspring (Vathy et al., 2007). The researchers found that disrupted maternal behavior was more important than prenatal drug exposure itself in rewarding cocaine self-administration in adulthood, especially in female offspring.

However, the late consequences of the in utero morphine exposure of female offspring were opposite to the consequences of the acute maternal effects. In particular, when these offspring became mothers, their active nursing behavior was increased; they were faster in carrying the first pup, returning the first pup to the nest and returning all pups to the nest (Slamberova et al., 2003).

## Opioid exposure during labor in human studies

Reynolds hypothesized that neuraxial analgesia is the worst type of analgesia for babies because of negative maternal changes

(e.g., maternal hypotension and fever, a prolonged second stage) (Reynolds, 2011). However, the fetal stress response to labor, resulting in a conspicuous catecholamine surge, is beneficial for adaptation to extrauterine life. Nevertheless, pain relief during childbirth is very common, so we have a large amount of human data.

Fentanyl (a synthetic opioid analgesic) is a frequently used, highly lipid soluble drug that would be expected to cross the placenta easily and to rapidly equilibrate between the maternal and the fetal circulation. However, the use of continuous-infusion epidural analgesia with low-dose bupivacaine and fentanyl over periods of up to 15 h during labor did not result in significant drug accumulation in either the mother or the neonate (Bader et al., 1995). Despite this fact, later consequences of opioid use during labor were present. Babies delivered after their mothers received >300 μg fentanyl during the last 4 h of labor may be at greater risk of respiratory depression (Kumar and Paes, 2003). Moreover, infants whose mothers received 80 μg sufentanil show mild neurobehavioral depression (Capogna et al., 1989). Several types of analgesia given to the mother during labor may interfere with the newborn's spontaneous breast-seeking and breastfeeding behaviors and increase the newborn's temperature and crying (Ransjo-Arvidson et al., 2001).

## Newborn exposure

### *Via the mother*

#### *Human data*

Milk production is a mammalian characteristic and is of particular importance for humans. In addition to their well-known nutritive role, milk constituents can carry specific information (Teschemacher et al., 1997). Thus, a number of milk protein fragments have been shown to behave as opioid receptor ligands. Most of these fragments have agonistic properties, and beta-casomorphins have known functional significance (Teschemacher and Koch, 1991). These peptides are implicated in a number of medical conditions, including diabetes, heart disease and symptoms of autism and schizophrenia, although the currently available data are inadequate to guide treatment recommendations (e.g., to eliminate the origin of casomorphin, casein, from the diet) (Christison and Ivany, 2006).

Recreational use of opioids exclusively during lactation is rare. However, maternal painkillers may have an effect on offspring. It is well documented that one of the overlooked effects of opiate use is an opiate-mediated elevation in the secretion of prolactin (Byrnes, 2005b). This elevation may lead to better milk production, which may partly compensate for harmful outcomes. In line with this observation, in one study, post-cesarean analgesia with epidural morphine had a relatively positive effect on offspring, who were more alert and oriented to animate human cues (Wittels et al., 1997).

#### *Animal studies*

Despite the possible positive effects in humans, Timar et al. found that in rats postnatal exposure to morphine through maternal milk resulted in slower weight gain and in males impaired habituation to a new environment (Timar et al., 2010). Moreover, the female offspring of morphine-treated lactating rat mothers (postnatal days (PNDs) 1–21) failed in a passive avoidance retention task (Nasiraei-Moghadam et al., 2013).

### *Direct infant exposure*

#### *Therapeutic usage in humans*

Both neonates and infants are able to mount a graded hormonal stress response to surgical interventions. Adequate intra- and postoperative analgesia not only modifies the stress response but also has been shown to reduce morbidity and mortality (Lonnqvist and Morton, 2005). Repetitive untreated pain and distress may impair the premature brain and have short- and long-term negative consequences (Duhrsen et al., 2013; Walker, 2014). For example, the effects of neonatal inflammatory pain resulted in decreased locomotor activity in adult rats, and this effect was reduced by morphine pretreatment (Bhutta et al., 2001). Therefore, pain management is increasingly recognized as an integral part of the effective management of vulnerable babies in the neonatal intensive care unit (NICU) (Walker, 2014; Hall, 2012). Beyond the most common non-pharmacologic techniques (sucking, maternal contact and massage), the drugs used to treat neonatal pain include opiates.

Nevertheless, opioid use poses a certain risk. The neuraxial administration of opioids may induce respiratory depression and increase the number of secondary medical interventions (due to postoperative nausea and vomiting, urinary retention and pruritus and decreased recovery of gastrointestinal function) (Hall, 2012; Lonnqvist et al., 2002). Morphine premedication for intubation leads to prolonged (24 h) electroencephalogram (EEG) depression, so this treatment is not recommended for short interventions (Norman et al., 2013). A high dose of opioids may induce EEG spikes, although behavioral convulsions are only rarely detected (van Praag and Frenk, 1992). Additionally, placebo-controlled trials in ventilated neonates found that fentanyl reduced stress hormones (catecholamines and glucocorticoids), episodes of hypoxia and behavioral stress scores but increased ventilation requirements (Anand and Hall, 2006). Moreover, morphine seems to provide adequate sedation and analgesia during hypothermia for the treatment of neonatal asphyxial encephalopathy (Roka et al., 2008). Taken together, several studies and reviews (e.g., Cochrane Reviews) have concluded that opiates should be used selectively in NICU newborns (Bellu et al., 2010).

#### *Experimental conditions in rodents*

Postnatal morphine administration may have negative effects on somatic development (including body growth and eye and vaginal opening development) (Zimmerman et al., 1977) and on neuronal growth in the developing animal (Hammer et al., 1989). Rozisky et al. observed that morphine treatment in early life in newborn male rats modulates brain-derived neurotrophic factor (BDNF) levels in the hippocampus (Rozisky et al., 2013). These changes may underlie behavioral alterations. Indeed, early postnatal exposure to morphine significantly decreased the ultrasonic vocalization of rat pups removed from their nest, serving as a marker of behavioral development (Cuomo et al., 1988). Moreover, repeated neonatal morphine injections in rats impaired passive avoidance learning and altered FST behavior in adulthood (McPherson et al., 2007).

Intraplantar formalin-induced pain reactions were reduced by acute morphine treatment in neonates (Abbott and Guy, 1995). However, when the postnatal morphine administration was followed by 4 days of abstinence, the pain reaction increased significantly (Zissen et al., 2006). Similarly, antinociceptive tolerance to morphine administration developed, as measured by a hot plate test (Bajic et al., 2013). In these cases, brain region-specific apoptosis occurred in unaffected glial cells, serving as a possible background mechanism (Bajic et al., 2013).

Controversially, the postnatal treatment of male rats with morphine reduced the development of pentylenetetrazol (PTZ)-induced seizures and the mortality rate in adulthood, possibly through the activation of GABAergic neurons in the hippocampus (Saboory et al., 2014). This effect was very similar to the consequences of prenatal morphine treatment, with decreased susceptibility to GABA-regulated seizures (Vathy, 2001). Additionally, morphine treatment may protect the developing brain from severe pain-induced pathological changes, although only under certain conditions (Duhrsen et al., 2013). Postnatal morphine treatment results in enhanced tail flick latency and a reduced ethanol preference, suggesting an additional positive impact (Duhrsen et al., 2013).

## Conclusions

The most common perinatal usage of opioids is for medical purposes, mostly in the form of a single or short-term treatment, and

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the main reason is to relieve pain. There is compelling evidence that an adverse intrauterine and postnatal environment can affect offspring's development and potentially lead to various learning, behavioral and mood disorders and to complex diseases, such as obesity and cardiovascular conditions, later in life (Schuurmans and Kurrasch, 2013; Rinaudo and Lamb, 2008; Viltart and Vanbesien-Mailliot, 2007). In particular, susceptibility to mental illnesses can increase (Fumagalli et al., 2007; Maccari et al., 2003). It is clear that repetitive painful experiences, such as randomly occurring invasive procedures and handling during neonatal intensive care, can permanently alter neuronal and synaptic organization and therefore later behavior (Anand, 2000). At the same time, analgesic drugs can be harmful, as morphine has been found to increase apoptosis in human fetal microglia and neurons (Hu et al., 2002). Whereas the short-term consequences of prolonged analgesic therapy in human neonates are well-known (tolerance, withdrawal and ventilator dependency), their long-term consequences are relatively unknown; animal studies suggest negative outcomes. Therefore, risk–benefit ratios should always be taken into consideration when pain relief is required in pregnant women or in neonates.

Recreational use of opioids can also alter many aspects of perinatal life; even the probability of conception may be disturbed. Intrauterine opioid exposure has many toxic effects (see above), leading to poor pregnancy outcomes, including underdevelopment, but it is believed that later negative consequences (Table 1) are more related to negative environmental factors (Ornoy et al., 1996; Weisglas-Kuperus et al., 1993). One of the crucial components is the disturbance of maternal care, which changes profoundly in substance-using mothers. Interventions will need to address the factors surrounding drug use to greatly improve neonatal outcomes (e.g., social circumstances, poor nutrition, stress, infections) (Schempf, 2007). Nevertheless, there is a certain optimum level of opioids, as not only opioid agonists but also antagonists have been shown to have long-term negative impacts (Farid et al., 2012). In dependent mothers, pre- and postnatal care initiation by society has special importance, and controlled treatment with a synthetic opioid (e.g., methadone or buprenorphine) could be beneficial (Kandall et al., 1999).

It is important to close the gap between scientific knowledge and societal programs for at-risk populations (Thompson et al., 2009; Walhovd et al., 2009). More emphasis should be given to disseminating scientific knowledge, enlightenment and prevention.

#### Conflict of interest statement

We disclose no possible conflict of interest in the conduct and reporting of research (e.g., financial interests in a test or procedure, funding by pharmaceutical companies for drug research).

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