

Prenatal and Perinatal Factors Influencing Nociception, Addiction and Behavior during Ontogenetic Development

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Summary

This review, which summarizes our findings concerning the long-term effects of pre-, peri- and postnatal factors affecting development, nociception and sensorimotor functions, focuses on three areas: 1) perinatal factors influencing nociception in adult rats were examined in rats with hippocampal lesions, after the administration of stress influencing and psychostimulant drugs (dexamethasone, indomethacine and methamphetamine); 2) the effect of pre- and early postnatal methamphetamine administration was shown to impair the development of sensorimotor functions tested in rat pups throughout the preweaning period; 3) the effect of extensive dorsal rhizotomy of the brachial plexus during the early postnatal period was studied with respect to neuropathic pain development and sensorimotor functions. The present study indicates that prenatal or neonatal stress, as well as various drugs, may disturb the development of the nociceptive system and cause long-term behavioral changes persisting to adulthood and that some types of neuropathic pain cannot be induced during the first two postnatal weeks at all. A mature nervous system is required for the development of the described pathological behaviors.

Key words

Nociception • Hippocampus • Methamphetamine • Rhizotomy • Ontogeny

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Introduction

It is generally accepted that the prenatal, perinatal and early postnatal periods are crucial and decisive for further ontogenetic development (Horn 1987, Campbell 1984). However, with respect to specific experimental conditions and the different mechanisms involved in the studied pathological symptoms and syndromes, it is possible to solve these mechanisms only partially. Therefore, we focused on: 1) the perinatal effects of several factors that could influence nociception in adult rats; 2) the development of chronic neuropathic pain in the early postnatal period; and 3) the development of sensorimotor functions in prenatally methamphetamine (MA)-treated rats.

Perinatal factors influencing nociception in adult rats

The developing nociceptive system is under the control of multiple endogenous and exogenous factors, e.g. neurotransmitters, neuromodulators, maternal care, maternal separation, prenatal stress, fostering and pre- and postnatally applied therapeutic or abused drugs.

Drugs administered in the perinatal period may interfere with gene expression during the determined program of developmental processes and thus disorganize perinatal ontogenesis, which is characterized by intensive cell differentiation and receptor formation in already

shaped organs (e.g. brain, immune and endocrine organs). These disturbances on the cellular or subcellular level are not evident at birth, but become apparent during further development and maturation as various neuro-psychobehavioral deviations.

All mediator systems that are involved in either pain transmission in the spinal cord (e.g. glutamate, substance P), pain suppression in the descending antinociceptive system (e.g. serotonin, noradrenalin, endorphins, enkephalins) or pain processing at the level of limbic or cortical structures (e.g. dopamine, endogenous opioids and cannabinoids) should be affected by perinatal manipulations.

Rats prenatally exposed to morphine exhibit greater tail-flick baseline values and higher analgesia in response to morphine challenge compared with control animals (Gagin *et al.* 1996). In adult rats prenatally exposed to morphine, increased withdrawal latency to thermal stimuli and an enhanced analgesic effect of morphine are also accompanied by a weaker effect of anxiolytic drugs (Voronina *et al.* 1994). These findings indicate that prenatal morphine induces long-lasting alternations in the opioid and serotonergic systems.

Selective serotonin reuptake inhibitors (SSRI) are widely used to treat antenatal and postpartum depression. Oberlander *et al.* (2005) found that infants with prenatal and postnatal SSRI exposure had diminished facial and cardiac autonomic responses to the pain of a heel-lance at 2 months of age. The observed blunted pain reactivity may reflect an increased or altered capacity to modulate pain signals as all SSRI are thought to increase synaptic serotonin concentration in the brain.

In our previous studies we evaluated the changes in nociceptive sensitivity to two drugs used in obstetrics and neonatology: indomethacin, given to risk newborns to prevent intraventricular haemorrhage or to accelerate the closure of patent ductus arteriosus, and dexamethasone, prescribed for the induction of surfactant production in immature fetal/neonatal lungs and thus for the prevention/treatment of neonatal respiratory distress syndrome. The experiments have shown that alterations in nociception appeared only following drug administration at a later stage of ontogenetic development (i.e. postnatal day (PD) 9-10). Indomethacin administration increased the sensitivity to thermal stimulus in 3-month-old rats; however, in old animals (12 months) these differences from controls disappeared. On the other hand, adult rats exposed to dexamethasone at PD9-10 revealed no changes in nociception at the age

of 3 months, but at the age of 12 months they showed decreased sensitivity in the plantar test and the tail-flick test (Benešová *et al.* 2001a,b). It could be assumed that the increase of latencies in old dexamethasone rats indicates an earlier onset of aging processes (Gagliese and Melzack 2000).

The last week of embryonic life and the first two postnatal weeks are critical periods in the development of the dopaminergic and serotonergic systems at which time they could be particularly vulnerable to injury (Galineau *et al.* 2004). The dopamine and serotonin transporters are also targets of many psychoactive drugs such as MA.

MA is a psychostimulant drug that acts on the central nervous system through a non-exocytotic mechanism, causing the release of monoamine neurotransmitters, including dopamine, noradrenaline and serotonin. Serotonin significantly influences the maturation of dendrites and synaptogenesis and plays a role in the regulation of brain development (Whitaker-Azmitia 2001).

As information about nociception in adulthood in prenatally MA-exposed humans as well as animals is missing, the aim of our experiments was to study this effect in adult Wistar rats whose mothers were exposed daily to stress (injection of saline) or to MA, either during their entire pregnancy or during pregnancy and lactation. MA and prenatal stress influenced nociception in adult male and female rats differently. It was found that females were more sensitive to the MA challenge to the mother and developed an increased sensitivity to pain, whereas males were more sensitive to prenatal stress without MA and developed a decreased sensitivity to pain (Yamamotoová *et al.* 2004). These results are in agreement with other studies showing gender differences in the impact of prenatal and postnatal stress on the magnitude of stress-induced opioid and non-opioid mediated antinociception in mice (Sternberg and Ridgway 2003).

The longer latencies observed in males born to mothers stressed with saline injections might reflect more intensive prenatal stress when compared with MA-exposed males. Although the stress intensity from a daily injection of MA or saline should be similar in both groups, MA might attenuate the physiological impact of acute stress (Söderpalm *et al.* 2003). Activation of dopamine receptors stimulates HPA-reactivity in rats, whereas glucocorticoids facilitate dopaminergic activity. However, when volume and cell number in the nucleus accumbens of adult offspring born to mothers who were

repeatedly stressed in mid-pregnancy by the injection of either saline or amphetamine were compared, no differences were found. Both groups had equally reduced volumes in comparison with intact controls (McClure *et al.* 2004).

The involvement of the hippocampus in pain processing has been described in several experimental studies and clinical observations in humans as well as in adult experimental animals (Hebben *et al.* 1985, Ploghaus *et al.* 2001). Less is known about the role of the hippocampus in nociception during development. A neonatal hippocampal lesion induced by ibotenic acid decreased latency in the hot plate and paw pressure tests (both supraspinally modulated), although no effect was observed in the tail flick test, which is mediated mostly at the spinal level (Al Amin *et al.* 2004). In another study focusing on postnatal hippocampal lesions, it was demonstrated that the behavioral outcomes of such lesions in rats are determined by early postnatal environmental variables, including social interactions (Wood *et al.* 2001).

Changes in the glutamatergic system resulting from neonatal brain infusion of quinolinic acid (QUIN) and/or *N*-acetyl-L-aspartyl-L-glutamate (NAAG) are thought to be important in animal models of schizophrenia. Comparing the two types of hippocampal lesions, we found that the perception of pain in these animals was influenced in different ways. Neonatal intracranial infusion of quinolinic acid did not change basal thermal nociception when compared with intact animals. The application of NAAG also did not significantly change nociception if compared with intact animals, but the latencies were longer than in QUIN-treated animals. Contrary to our expectation, significant differences were observed between sham-operated rats living with QUIN-treated animals and those living with NAAG-treated animals. Our results show that social factors, which were originally demonstrated only in pain behavior, might also influence basal nociceptive sensitivity in rats (Yamamotová *et al.* 2007).

Nociceptive sensitivity should not be considered exclusively innate even if the animals housed together are siblings, because identical changes were observed in rats coming from different families. These results suggest the possibility of transferring some patterns of behavioral abnormalities (including pain sensation) from more pathologic individuals to more vulnerable ones during the period of pre-adolescent development.

Our experiment with cross-fostering in prenatally

MA-treated rats and prenatally saline-treated (stressed) rats showed that nociceptive sensitivity is dependent on social factors and therefore can be affected by the quality of maternal care (Yamamotová and Šlamberová 2005). Prenatally MA-treated male rats fostered by adoptive stressed mothers had higher sensitivity to pain than prenatally stressed rats fostered by MA mothers. Rats fostered by their own mothers did not differ in nociception. Differences in nociception in rats fostered by adoptive mothers might result from changed stress reactivity, which has long-term consequences on their behavior and emotionality. Repeated maternal separation during the first week of life also alters the antinociceptive effect of morphine. Maternally separated rats exhibited exaggerated behavioral and neuroendocrine responses to stress in adulthood in comparison with controls, and the antinociceptive effect of morphine was less potent. However, this effect was observed in the hot-plate test but not in the tail-flick test (Kalinchev *et al.* 2001).

The observed results support the hypothesis that variation in rat maternal care could serve as a mechanism for a non-genomic behavioral mode of the transmission of traits.

Effect of perinatal MA exposure on the sensorimotor development of rat pups

One of the most serious problems of the present day is drug, alcohol, and nicotine abuse. The percentage of drug abusers is growing from year to year and their age is getting lower. While many clinical and experimental studies have investigated behavioral and biological changes in drug-abusers, there is not much known about the effect of drug abuse in pregnant women and the possible long-term effects of prenatal drug-exposure on their progeny during development and in adulthood. However, statistics show that the number of infants with drug-related birth defects has increased dramatically over the past several years (Marwick 2000). Drugs easily cross the placental barrier and therefore may affect the development of the fetus. Furthermore, the newborns may also receive these drugs postnatally in the mother's breast milk. The drug abuse of pregnant women and mothers is therefore not only a serious social problem, but also a serious health problem that is necessary to deal with.

Beside direct effects, drugs also have indirect ones. It was shown that drug-abusing women are less scrupulous in the prenatal as well as the postnatal care of their children (Vavřínková *et al.* 2001). Ninety percent

are single mothers and generally deliver at younger ages than mothers who do not abuse drugs. They are often unemployed women with economic and social problems and are not able to take good care of their children. This usually results in the legal system's removing the child from the drug-abusing mother. All of this may lead to psychological deprivation and the mental retardation of the child. Thus, not only drug abuse itself, but also worse maternal care may induce irreversible changes in the development of children.

In agreement with clinical works, experimental studies (Bridges *et al.* 1982, Fraňková 1977, Šlamberová *et al.* 2001, 2003, 2005, 2007) demonstrated that rat mothers who received drugs during the period of gestation and/or lactation displayed decreased maternal behavior toward their pups. In addition, our and other studies have shown that perinatal drug exposure impairs the postnatal development of rat pups (Acuff-Smith *et al.* 1996, Martin *et al.* 1976, Šlamberová *et al.* 2005, 2006, 2007). The extent of the drug-induced effect and the extent of the effect induced by decreased maternal care on healthy pup development remain, however, unclear.

Postnatal care plays an important role in the emotional and cognitive development of children. Physical and emotional deprivation and family conflicts may induce long-term consequences in the postnatal development of a child (Meaney 2001). Children who have been exposed to abuse or neglect are more likely to develop numerous psychopathologies, such as anxiety, mood disorders and psychosis, that might persist throughout life (Bebbington *et al.* 2004). In mammals, the mother is the principal caregiver, providing both nutritional resources and behavioral stimulation to her offspring. In the rat, maternal care during the first week of postnatal life, particularly licking/grooming (LG), influences hippocampal development and function (Liu *et al.* 2000). Liu *et al.* (2000) showed that the offspring of mothers who exhibited a higher frequency of LG over the first week of postnatal life had increased hippocampal synaptic density and enhanced spatial learning and memory. In addition, Meaney (2001) found that female rat pups that received increased maternal care were also „better mothers“ in adulthood than female offspring of mothers exhibiting neglectful maternal behavior. Thus, it was shown that postnatal care plays an important role in the development of offspring. The question, however, is whether maternal care may improve the drug-induced impairment of postnatal development.

There are only a few studies showing the effect

of cross-fostering on the postnatal development of offspring exposed prenatally to a drug or alcohol. In alcohol studies, Lancaster *et al.* (1984) demonstrated that the offspring of control dams cross-fostered during lactation to ethanol-treated dams had abnormal organ weights, abnormal brain weights and severely depressed brain myelin concentrations. Vorhees (1989) showed that fostered offspring oriented to their home cage scent less than did cross-fostered offspring and also that cross-fostered animals were more active than fostered animals in an open field test. Murillo-Fuentes *et al.* (2001) showed that chronic alcohol administration during gestation and/or lactation adversely affects pup growth prior to weaning as indicated by its effect on milk consumption, pup and organ weight.

There are no studies available that would show how maternal care may affect the postnatal development of animals prenatally exposed to drugs. Our most recent results (Hrubá *et al.* 2008) indicate that prenatal and postnatal MA exposure impairs the postnatal development of rat pups, especially sensorimotor functions and postural reflexes. Our previous studies (Šlamberová *et al.* 2006, 2007) showed that MA administered during prenatal and/or preweaning periods alters the functional development of rat pups and also that it alters two generations of offspring. This impairing effect of MA seems to be improved by postnatal care from control mothers. Specifically, prenatally MA-exposed pups fostered by control dams were significantly better in a righting reflex test on a surface and a rotarod test than either prenatally or postnatally MA-exposed pups. Prenatally MA-exposed pups fostered by controls or saline-exposed dams were faster in righting than either prenatally or postnatally MA-exposed pups. Further, in the rotarod test, prenatally MA-exposed animals fostered by controls or saline-exposed dams displayed a similar time on the rotating cylinder relative to controls or saline-exposed pups. In a negative geotaxis test, pups prenatally exposed to MA and raised by control mothers had a faster latency of turning, but these results were not significant (Hrubá *et al.* 2008).

On the other hand, our data (Hrubá *et al.* 2008) demonstrate that control pups postnatally exposed to MA displayed worse results in all tests than did controls or prenatally saline-exposed pups fostered by controls or saline-exposed pups. The ability of pups to right themselves on a surface and in mid-air was worse in control pups postnatally exposed to MA than in controls or prenatally saline-exposed pups fostered by controls or

saline-exposed dams. Control pups that were fostered by MA-treated mothers spent less time on the rotating cylinder and had longer latency of turning in negative geotaxis test than control pups fostered by control mothers.

A possible explanation of the impairing effect of drugs and alcohol on sensorimotor functions might be alterations in myelin development. This hypothesis is supported by the findings of Lancaster *et al.* (1984), who demonstrated an impairing effect of ethanol administered during gestation and lactation on myelin development. When animals born to dams consuming ethanol during gestation were cross-fostered to control dams at birth, myelin development was comparable to that of the offspring of pairfed and well-nourished controls. On the other hand, when the pairfed or nourished pups were cross-fostered at birth to lactating dams consuming ethanol, myelin development was more severely depressed than myelin development in pups cross-fostered to pairfed lactating dams.

Thus, it seems that the postnatal care provided by a control mother at least partially improves the development of rat pups prenatally exposed to drugs.

Chronic pain in the early postnatal period

Neuropathic pain is known to appear in infants and younger children, although the incidence is much lower than in school-age children and adults. The lesion of the nervous system can be either peripheral or central. Peripheral neuropathic pain in newborns and children consists mostly of complex regional pain syndrome, scar neuroma and phantom limb pain (Wilder *et al.* 1992, Ingelmo and Fumagalli 2004). Central neuropathic pain (Al Qattan 1999, Rossitch E Jr *et al.* 1992) in newborns and children consists mostly of brachial plexus lesions, which might evoke severe self-mutilation in total avulsion.

There are only a few papers dealing with the effect of total or partial deafferentation on pain during the postnatal period in rats (Vaculín *et al.* 2005, Howard *et al.* 2005, Lee and Chung 1996).

The brachial plexus is the most common site involved in upper extremity neuropathies in human neonates. The incidence of a brachial plexus lesion (BPL) in neonates varies between 0.03 and 1%. BPLs in neonates have been traditionally divided into three groups according to the affected roots as follows: Erb's (C5-C6, ev. C7; most common), Klumpke (C8-Th1; the lowest

incidence) and total (Dodds and Wolfe 2000). A BPL in neonates impairs sensory and motor functions and sometimes evokes self-mutilation, which is severe in patients with a total lesion and usually consists of biting the tips of the digits (Al Qattan 1999, Rossitch E Jr *et al.* 1992). The pathological mechanisms of these injuries remain unclear; however, high birth weight, shoulder dystocia and forceps-assisted deliveries have been identified as risk factors.

A model of brachial plexus avulsion – multiple dorsal rhizotomy in rats – was introduced by Basbaum (1974). A unilateral dorsal rhizotomy of the brachial plexus nerves (C5-T1 deafferentation) is known to induce self-mutilation in rats. There are conflicting views about the correlation between self-mutilation and pain sensation in animal models (Rodin and Kruger 1984). However, evidence points to the theory of self-mutilation as a behavioral correlate of pain sensation (Lombard *et al.* 1979, Mailis 1996, Sweet 1981, Vaculín and Rokyta 2004).

Total deafferentation, as a model of central neuropathic pain, has been performed in the early postnatal period in rats and, in general terms, the effect is much smaller than in adults (Vaculín *et al.* 2005). In terms of motor function, only occasional misplacement is noticeable. Sitting down on its hind legs, the rat keeps the deafferentated forelimb in extension, but when the forelimb is to be used again, no visible differences are noticed. Programmed behavior (grooming) is identical with that of intact animals. When feedback sensation from proprio- and exteroceptors is not required for precise movement, no visible differences in movement can be observed.

In terms of pain syndrome, self-mutilation does not develop at all when total deafferentation is performed prior to PD 21; slight symptoms appear when the deafferentation is performed between PD 21 and PD 35, and self-mutilation similar to that observed in adults develops when the deafferentation is performed after PD 35.

Similar results were described by Howard *et al.* (2005) in two peripheral neuropathic pain models. They used spared nerve injury (SNI) and chronic constriction injury (CCI) models to observe pain development in rat pups. The SNI model is evoked by tight ligation and sectioning of two of the three branches (tibial and common peroneal nerves) of the sciatic nerve, while leaving the third branch (sural nerve) intact. SNI induces mechanical allodynia and other signs of neuropathic pain in adult animals (Decosterd and Woolf 2000). In contrast,

SNI performed in animals aged 3, 10 or 21 days does not evoke allodynia. Only SNI performed at PD 33 or later leads to persistent allodynia with the threshold falling more than 50 % of control values (Howard *et al.* 2005). CCI is evoked by four loose ligations placed around the sciatic nerve and induces mechanical and thermal allodynia and hyperalgesia in adult rats (Bennett and Xie 1988). In contrast, CCI evoked by the placement of three ligatures induces no changes in mechanical pain thresholds (Howard *et al.* 2005).

On the other hand, Lee and Chung (1996) described the development of mechanical allodynia in 7-, 14- and 21-day-old rats following spinal nerve ligation. Spinal nerve ligation is evoked by tight ligation of the L5 and L6 spinal nerves and triggers neuropathic pain behavior in adult rats (Kim and Chung 1992). When performed in the early postnatal period (in the youngest two groups), however, allodynia disappeared several weeks after the surgery in contrast to adults.

In all the described models, pain testing is based on motor performance. Therefore, it was suggested that the immaturity of the motor system prevents testing until 15 days of age since the rats cannot stand or walk before this time point. However, it was shown by many authors that a paw withdrawal reaction appeared even before that time. The first reflexive respond to somatic stimulation appears on the 15th gestational day in rats (Narayanan *et al.* 1971). At the same time spontaneous movement might be detected (de Vries *et al.* 1982). However, the stimulation is of a tactile or pressure nature rather than a nociceptive modality (Fitzgerald 1987). Rat pups are able to express pain behaviour immediately after birth. It was shown that pain behavior appears in one-day-old rat pups when exposed to a formalin test (Abbott and Guy 1995). Pain thresholds determined as a response to thermal and/or mechanical stimulation were demonstrated to be lowest on postnatal day 1, then the thresholds increase until PD 7 and remain unchanged afterwards (Tseng 1998). However, other authors described either a decrease in the latency to thermal nociceptive stimulation from PD 10 to PD 25 (Ba and Seri 1993) or peaks of minimal latency at PD 7 and maximal latency at PD 15 (Hassmannová and Rokyta 2002). Therefore, it seems very likely that the absence of paw withdrawal changes after the induction of peripheral neuropathic lesions is rather linked to factors involved in neuropathic pain development. These factors develop between the second and third postnatal weeks and might be attributed to sympathetic innervation, ectopic discharges,

involved receptor immaturity, the descending pain inhibitory system, synaptic reorganization, and other causes (Lee and Chung 1996, Vaculín *et al.* 2005, Howard *et al.* 2005).

The central nervous system in the rat matures around the third postnatal week, and the maturation and rearrangement of NMDA receptor subunits and function occur around the 30th postnatal day (Alvares and Fitzgerald 1999, Fitzgerald and Jennings 1999, Gonzalez *et al.* 1993). In several studies (Vaculín and Rokyta 2004, Tseng 1998, Wong *et al.* 1998, Yoshimura and Yonehara 2006, Yashpal *et al.* 2001) it was shown that neuropathic pain in an adult rat is not likely to develop when the NMDA receptors have been blocked. Accordingly, it was suggested that the structural and functional rearrangement of NMDA receptors after birth might be one of the most important factors underlying neuropathic pain development in young animals (Vaculín *et al.* 2005).

Conclusions

From our results we can conclude that prenatal or neonatal stress, as well as various drugs, may disturb the development of the nociceptive system and cause long-term behavioral changes persisting to adulthood. The development of neuropathic pain behavioral symptoms in rats strongly depends on the period of nervous system injury, and a mature nervous system is required for the development of the described pathological behavior. However, we obviously do not know all the involved factors, and therefore further studies performed during the early postnatal period are required.

Future studies will investigate the effect of perinatal exposure on adult rats. Behavioral tests, such as the open field test, and tests of anxiety, such as the elevated plus-maze, will be used to detect long-term changes in behavior induced by perinatal drug exposure and the possible effect of maternal care. Because gonadal hormones have been shown to affect anxiety and behavior especially in female rats, both males and females (with consideration of the stage of their estrous cycle) will be used in all experiments.

Conflict of Interest

There is no conflict of interest.

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