Variation in Plasma Morphine Level and Pain Sensitivity in Prenatally Morphinized Rats

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It is established that mature random-bred and Wistar rats exhibit the same level of pain sensitivity in the tail-flick test, but the analgetic effect of morphine (5 mg/kg) is variously expressed: marked hypalgesia is observed in mongrel but not in Wistar rats. Prenatal morphinization enhances the analgetic effect of morphine in both mongrel and Wistar rats. There is a direct correlation between the plasma morphine content in prenatally morphinized rats and their sensitivity to the analgetic action of morphine.

Key Words: *morphine; prenatal period; offspring; pain sensitivity*

A reduced pain sensitivity has been demonstrated in offspring of random-bred female rats injected with morphine during pregnancy [1,5]. This effect may be attributed to both a reduced number of opioid receptors [10] and disturbed morphine pharmacokinetics in the brain. However, the changes in the pharmacokinetics of morphine in prenatally morphinized offspring remain poorly understood. It is possible that morphine, which readily crosses the placental barrier [2,3] and enters the developing fetus, is able to modify the activity of enzyme systems involved in opiate metabolism in children and adults. The aim of the present study was, first, to elucidate whether pharmacokinetic mechanisms govern the changes observed in prenatally morphinized rats and, second, to compare the nociceptive reaction in genetically different Wistar and mongrel rats.

MATERIALS AND METHODS

The experiments were carried out in male Wistar and mongrel rats, whose mothers were injected with morphine in a dose of 10 mg/kg every 12 hours from the 9th to the 19th day of gestation. The mothers of controls were injected with the same volume of 0.9% NaCl at the same times of gestation. The nociceptive reaction was evaluated in the tail-flick test by the latency of tail withdrawal in response to a thermal stimulus. After determination of the background pain sensitivity, 2.5-month-old offspring were intraperitoneally injected with morphine hydrochloride in a dose of 5 mg/kg and the latency of the pain reaction was redetermined. In male Wistar pups the background pain sensitivity was also determined at the age of one month. In 12 Wistar rats (6 experimental animals and 6 controls) the plasma concentration of morphine 10 min after intraperitoneal injection in a dose of 20 mg/kg was measured by high performance liquid chromatography [9] in our modification. The results were processed statistically using the Student t test.

RESULTS

A reliably decreased pain sensitivity was observed in prenatally morphinized mongrel 2.5-month-old mongrel rats. Morphine injection increased the latency of the nociceptive reaction more than 2-fold in mongrel rats, both prenatally morphinized and controls. However, the latency in prenatally morphinized

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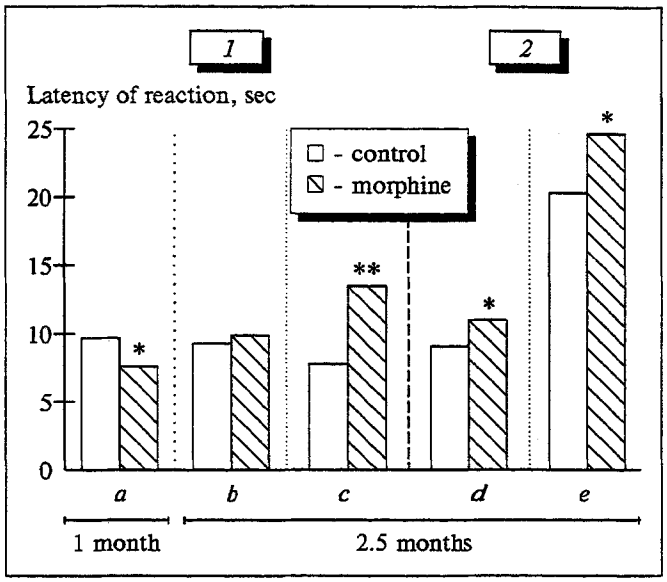

Fig. 1. Pain sensitivity to a thermal stimulus in the tail–flick test in prenatally morphinized rats. Abscissa: age at the time of testing. *1*) background, *2*) after administration of 5 mg/kg morphine; *a, b, d*) Wistar rats, *c, e*) mongrel rats. $^{*}p<0.05$, $^{**}p<0.01$ in comparison with the control.

rats was reliably longer than in controls (Fig. 1). In contrast, in prenatally morphinized 2.5-month-old Wistar offspring pain sensitivity to the thermal stimulus did not differ from that in controls. However, in younger (1-month-old) prenatally morphinized Wistar rats (Fig. 1) the pain sensitivity threshold was reliably lowered. When morphine (5 mg/kg) was injected to Wistar controls, a tendency toward hyperalgesia was observed, while in prenatally morphinized animals the latency of tail withdrawal was reliably increased (Fig. 1). Consequently, prenatal morphinization increases the sensitivity of both Wistar and mongrel rats to the analgetic effect of morphine. An increased sensitivity to morphine in rat offspring has also been demonstrated using prenatal treatment with methadone [6]. The changed reaction in morphinized offspring is probably due to suppressed activity of the metabolic systems of the organism due to long-term contact with morphine. To verify this assumption we carried out pharmacokinetic studies in prenatally morphinized 2.5-month-old rats. It was found that 10 min after intraperitoneal injection of 20 mg/kg morphine its plasma content was 1.42±0.13 μg/ml in prenatally morphinized Wistar rats, whereas in control animals it was considerably lower, 0.89±0.14 μg/ml. Thus, a correlation exists between elevation of the pain threshold and an increase in the plasma content of morphine. Morphine delivered to the fetus evidently inhibits the opiate-metabolizing enzyme systems of the liver, affecting the functioning of the opioid system, the threshold of pain sensitivity, and the reaction to morphine. Another mechanism underlying the changes in pain sensitivity to morphine in prenatally morphinized rats is direct interference with the activity of the opioid receptors.

The dependence between changes in pain sensitivity in prenatally morphinized rats and the genetic characteristics and age is of fundamental importance. For instance, hyperalgesia was noted in one-month-old but not in 2.5-month-old Wistar rats, while in mongrel 2.5-month-old rats we observed hypalgesia to the thermal stimulus. On the other hand, random-bred and Wistar rats are characterized by a different initial sensitivity to the analgetic effect of morphine (5 mg/kg): marked hypalgesia in the former and no effect in the latter. The differences are presumably due to peculiarities of the opiate system in the tested strains, as is confirmed by the data obtained on other animal species. For instance, the effect of morphine on pain sensitivity was found to vary in roosters of different breeds [8]. Administration of morphine induced analgesia in Rhode Island Red birds (650) and hyperalgesia in White Leghorns (937) and Cal-Whites (542). This phenomenon can be attributed to the fact that selection of breeds results in a relative prevalence of κ-opioid receptors in breeds 937 and 542, and activation of these receptors may cause hyperalgesia. Age-related peculiarities of the analgetic effect of morphine in rats have also been demonstrated [4]: in 8-week-old animals the effect was reported to be weaker than in 24-week-old ones.

Thus, morphine in a dose of 5 mg/kg exerts an unequal analgetic effect in rats of different lines: marked hypalgesia in random-bred rats and no such effect in Wistar rats. The analgetic effect of morphine is enhanced in both mongrel and Wistar prenatally morphinized rats. This correlates with a higher plasma concentration of morphine in these animals in comparison with controls.

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