GENETICS

Nociceptive Thresholds in Adult Rats of Three Strains after Pain Stimulation in the Neonatal Period

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Nociceptive thresholds in the tail-flick test decreased in adult 2.5-month-old KM, Wag/Rij, and Wistar rats receiving injections of placebo in the neonatal period (days 3-9 of life).

Key Words: *pain sensitivity; neonatal period; inbred rats; behavioral genetics*

Administration of pharmacological preparations and bioactive substances to rats and mice in the neonatal period modulates behavioral characteristics and physiological state of adult animals [1,2,6]. We previously evaluated the effects of treatment with some substances in the neonatal period on physiological parameters of adult animals [4]. These experiments were performed with control animals receiving placebo (physiological saline or distilled water). Testing after attaining adulthood revealed changes in nociceptive thresholds (NT) of these animals. Clinical observations indicate that pain stimulation in the neonatal period produces delayed consequences [4,5]. Here we studied the effects of painful stimulation in the neonatal period on NT in adult rats.

MATERIALS AND METHODS

Experiments were performed on KM, Wistar, and Wag/Rij rats. Previous studies showed that practically 100% KM rats display audiogenic convulsions during sound stimulation. Wag/Rij rats are characterized by absence epilepsy with spontaneous generalized peak-wave seizures in EEG. Series I was performed on 127 male and female KM (n=99), Wistar (n=15), and Wag/Rij rats (n=13) from 16, 6, and 3 litters, respectively. Series II was performed on 30 male and female KM (n=9), Wistar (n=11), and Wag/Rij rats (n=10) from 5, 4, and 4 litters, respectively. Series III was performed on 32 KM rats from 12 litters.

Painful stimulation (subcutaneous injection of placebo) was performed daily on days 2-6 (series I), 3-9 (series II), and 2-7 of life (series III). Physiological saline (series I and III) or distilled water (series II) were administered in a volume of 20 ml.

NT in adult 9-11-week-old animals was estimated half-automatically by the tail-flick latency during thermal stimulation of the skin with light beams. In series I, II, and III testing was repeated 3-5 times at various intervals. The mean tail-flick latency was calculated.

We revealed no differences in the effect of painful stimulation during the neonatal period in males and females. Therefore, the data on males and females were pooled.

The results were analyzed by Mann—Whitney U test.

RESULTS

Painful stimulation in the neonatal period decreased thermal NT in Wistar and RM, but not in Wag/Rij rats (Fig. 1). NT in KM rats decreased insignificantly in series II, which was probably related to low number of animals.

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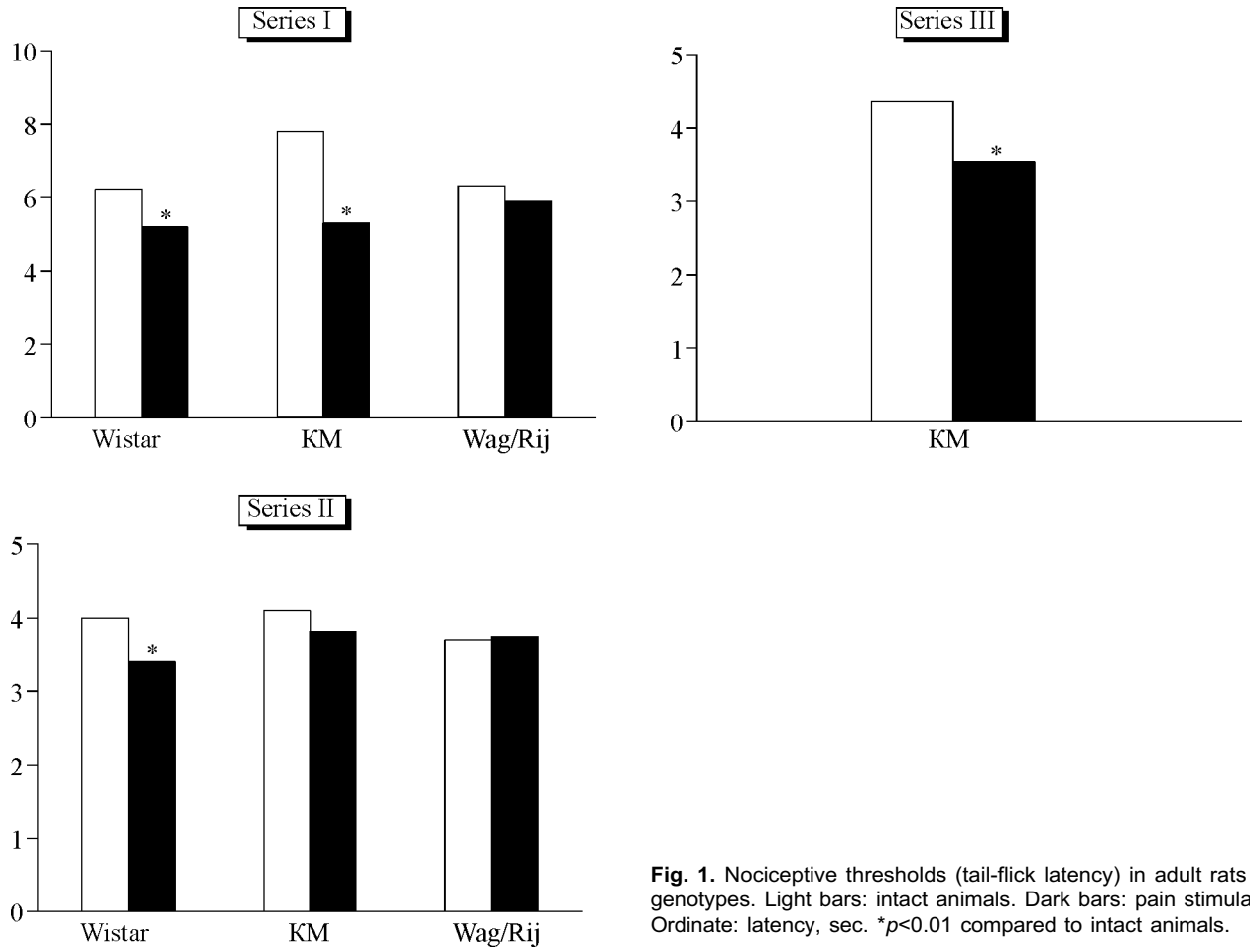

Fig. 1. Nociceptive thresholds (tail-flick latency) in adult rats of 3 genotypes. Light bars: intact animals. Dark bars: pain stimulation. Ordinate: latency, sec. *p<0.01 compared to intact animals.

Our results showed that administration of placebo in the neonatal period (pain stimulation from the 2nd to 7th days of life) produced tail-flick hyperalgesia in adult Wistar and KM, but not in Wag/Rij rats. The absence of changes in NT in Wag/Rij rats was probably associated with genetic disturbances in the opioidergic system [7]. In series II administration of placebo served as the control for neonatal treatment with ketamine. Ketamine produced a greater decrease in NT, which was observed also in Wag/Rij rats [4]. Moreover, painful stimulation in the neonatal period affected the sensitivity to sound stimulation (audiogenic epilepsy) in KM, Wag/Rij, and Wistar rats. These data suggest that painful stimulation in the neonatal period produced serious delayed consequences.

Single painful stimulation or administration of substances produces long-lasting changes in the development of the nociceptive system in the brain. This treatment is followed by different changes in rats with various genotypes. Our results are consistent with published data on the existence of interlinear differences in the effects of $ACTH_{4-10}$ administration to mice in the neonatal period [3].

Treatment of control animals in the neonatal period produces delayed consequences, which should be taken into account in evaluating the effects of biologically active substances during the development of CNS.

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