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GENETIC AND SEASONAL DIFFERENCES IN THE EFFECT OF STRESS ON PAIN SENSITIVITY IN MICE

N. K. Popova and L. A. Koryakina

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Evidence has recently been obtained to show that different types of stress modify pain sensitivity, by inducing poststress analgesia [4, 5, 9]. Lowering of sensitivity to pain has been observed in rats and mice with different models of stress: electric shock [9], restricted mobility [5, 7], swimming in cold water [11], or injection of formalin [4]. At the same time, there are reports that chronic [9] and acute stress [8, 12] induce hyperalgesia. It is not yet clear to what these differences in the character of changes in sensitivity to pain can be attributed. The writers have suggested that they may depend on the animal's genotype. It must be pointed out that investigations into the effect of stress on sensitivity to pain have mainly been undertaken on animals of the same lines, and the role of genotype has thus remained unstudied. Possible effects of seasonal factors on stress-induced changes in sensitivity to pain likewise have not been studied.

In the investigation described below the role of genetic mechanisms and seasonal factors in poststress changes in sensitivity to pain were studied in inbred lines of mice.

EXPERIMENTAL METHOD

Male mice of ten inbred lines (BALB/c, C57Bl/6J, AKR, DD, A/He, DBA1, CBA, CC57BR, DBA/2J, C3H/He), aged 2.5-3 months and weighing 20-26 g, were used. The animals received food and water *ad lib*. The mice received thermal burns from a hot plate [6]. The animals were placed on a metal cylinder (diameter 18 cm, height 15 cm), the surface temperature of which was maintained at 55±1°C by means of an ultrathermoscope. The mice could leave the plate. Sensitivity to pain was estimated from the latent period of the avoidance reaction, i.e., the duration of the animal's stay on the hot plate, in seconds.

Emotional stress was induced by restricting movements of the mice by placing them in unfamiliar constraining cages 2.5 cm in diameter and 8 cm high for 30 min. The effect of seasonal factors was studied on mice of 7 lines. The experiments were carried out throughout the year: in winter (January, February), in spring (March, April), in summer (June), and in the fall (September, October).

The experimental results were subjected to dispersion analysis and correlation analysis by standard methods [3].

EXPERIMENTAL RESULTS

Marked interlinear differences were found in the effects of emotional stress on sensitivity of the mice to pain (Table 1). Stress induced by restriction of the animals' movements for 30 min changed the duration of the subsequent stay of mice of 5 lines on the hot plate. The antinociceptive effect of stress was observed under these circumstances in two lines (DD

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TABLE 1. Effect of Emotional Stress (hot plate, 55°C) on Sensitivity of Inbred Lines of Mice to Pain (M ± m, n = 20)

Line of mice	Latent period of avoidance reaction, sec	
	Initial	Restriction of movements for 30 min
CC57BR	13,0±1,8	14,0±2,4
C57Bl/6J	15,0±1,8	16,0±2,2
DD	20,0±2,1	48,0±3,9 (14 %)
DBA1	29,0±2,2	29,0±4,7
A/He	30,0±2,9	19,0±2,2 (63 %)
AKR	31,0±2,5	25,0±2,2
BALB/c	37,0±3,5	25,0±2,6 (68 %)
C3H/He	57,0±5,1	65,0±6,6
DBA/2J	82,0±14,0	42,0±9,9 (51 %)
CBA	97,0±19,4	148,0±19,0 (48 %)

Legend. Changes, in per cent of corresponding control, taken as 100, shown in parentheses ($P < 0.05$).

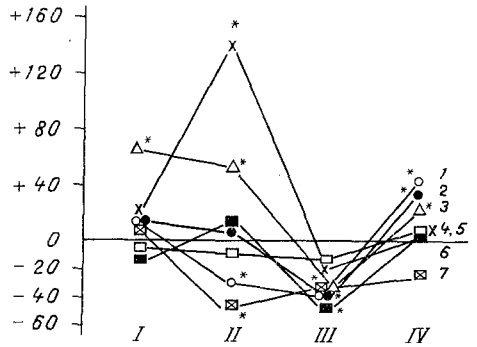

Fig. 1. Seasonal changes in effects of emotional stress on sensitivity of mice to pain. Ordinate change in latent period of avoidance reaction (in per cent). 1) BALB/c; 2) C57Bl/6J; 3) CBA; 4) AKR; 5) DD; 6) CC57BR; DBA/2J.
* $P < 0.05$ compared with initial nociceptive response. I) Winter, II) spring, III) summer, IV) fall.

and CBA), whose threshold of sensitivity to pain was increased by 140 and 52% respectively. In mice of lines BALB/c, A/He, and DBA/2J sensitivity to pain was increased after restriction of movement: The length of stay of mice of these lines on the hot plate was reduced by 32, 36, and 49% respectively. The duration of stay of these mice on the hot plate was unchanged by the action of stress. Dispersion analysis revealed highly significant interlinear differences in the action of emotional stress on sensitivity of mice to pain ($F = 21.9$; $P < 0.001$). Incidently, the character of the poststressor changes in sensitivity to pain was independent of the initial response. For instance, in DD mice the initial nociceptive response was weak, whereas in CBA mice it was strongest of all, but in animals of both these lines emotional stress was accompanied by analgesia. Hypersensitivity after stress also was found in lines of mice responding differently to pain.

Thus besides the analgesic effect of stress, hyperalgesia and no effect of stress on sensitivity to pain were both found. These differences in the character of the effect of emotional stress nociceptive sensitivity depended on the animals' genotype, for the experiments were standard and were carried out during the same season (in spring), but on mice of different lines, i.e., of different genotype. Consequently, genotypic differences are an important factor determining not only the severity of the poststress changes in sensitivity to pain, but also the character of these changes.

Seasonal factors also had a significant effect. In all lines studied considerable seasonal changes were observed in the effects of stress on sensitivity to pain (Fig. 1). In summer an antinociceptive action of stress could not be found in any of the 7 lines studied; in mice of 3 lines there was a significant increase in sensitivity to pain, and in the rest a tendency toward such an increase. Meanwhile in the fall considerable changes took place in the character of the effects of stress on sensitivity to pain: The analgesic effect of emotional stress was observed in mice of 3 lines (BALB/c, C57Bl/6J, CBA), but hyperalgesia was not found in a single line. The greatest polymorphism as regards the effects of stress on sensitivity of mice of different lines to pain, was observed in spring.

Among the lines studied some responded strongly, others weakly to stress, but in no case did the animals of a particular line not respond to stress by a change in sensitivity to pain during at least one season.

The predominantly analgesic action of stress has been described in the literature [4, 5, 7, 9, 11]. However, there is information that the intensity of the antinociceptive action may differ for different types of stress [5, 8], and that depending on the type of stressor, not only analgesia but also hyperalgesia may arise [8, 10, 12]. These facts accord with the view that the body's response depends on the nature of the stressor [1,2]. However, we have found two other factors which determine the character of poststress changes in sensitivity to pain. Significant differences were found in mice of different genotypes in their response to the same types of stress, evidence of the important role of hereditary mechanisms, and seasonal factors and rhythms were shown to have a marked influence on the manifestation of the effects of stress on sensitivity to pain.

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