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COMMUNICATIONS

Brain dopamine and jumping behaviour in mice

One of the remarkable signs of the abstinence syndrome precipitated in morphine-dependent mice by administration of narcotic antagonists is the stereotype jumping behaviour (Maggiolo & Huidobro, 1961). This behaviour has been widely used as an index for estimating the degree of narcotic dependence (Way, Loh & Shen, 1969; Sealens, Granat & Sawyer, 1971; Takemori, Stesin & Tulunay, 1974). Change in the brain dopaminergic system was suggested as one of the possible mechanisms of jumping behaviour induced by narcotic antagonists (Iwamoto, Ho & Way, 1973; Maruyama & Takemori, 1973). Recently, simulation of naloxone-induced jumping by drugs which have an effect on the dopaminergic system in the brain was reported by Collier, Francis & others (1974), Colpaert & Lal (1974) and Lal, Colpaert & Laduron (1975). These results further indicate that brain dopamine is involved in jumping behaviour. However, although the jumping syndrome and increase in brain dopamine concentrations are recorded after administration of narcotic antagonists, there is little information on the mechanism involved in such motor behaviour. In the present investigation the jumping syndrome was produced by two different methods; one was induced by administration of naloxone to mice treated acutely with morphine, the other was induced by high ambient temperature. The effect on the concentration of brain dopamine and the changed motor behaviour of experimental animals subjected to two different methods, studied in a time-course manner, should give some information about the mechanism of stereotyped jumping behaviour.

Male Wistar strain mice, 20 to 26 g, were injected subcutaneously with morphine or saline and 2 h later received either naloxone (kindly supplied by Endo Laboratories) or saline. They were placed in a glass jar (20 cm diameter, 45 cm high), and the number of jumps was counted during the next 10 min. Lifting of four legs simultaneously was taken as the criterion of jumping. Two mice were placed in the glass jar at the same time. When high ambient temperature was used, an infrared lamp hanging over the top of the jar was used as the source of heat. The temperature was kept at $36 \pm 1°$ by changing the voltage. At the temperature lower than 36° the animals did not jump, and higher temperature resulted in severe salivation. Way, Loh & others (1974) also used 36° in studying the withdrawal syndrome produced by naloxone in morphine-dependent mice. Estimation of dopamine and noradrenaline was followed using the method of Shellenberger & Gordon (1971). Mice were killed at various times after the injection of naloxone or saline, and after they were placed in the glass jar. The forebrain area, which consisted of cerebral hemispheres including corpus striatum, was collected and homogenized in 0·4 N perchloric acid. The homogenates were centrifuged, and the supernatants were used for the assay of dopamine and noradrenaline.

In the present study, we demonstrated that the jumping can be produced in mice by high ambient temperature as well as by naloxone (25 mg kg^{-1}), administered to mice pretreated with 100 mg kg^{-1} of morphine sulphate for 2 h. Also, similar behaviour, such as the increase in locomotor activity, or rearing of hind legs before jumping, was observed in both groups. The height of jumping seemed also to be the same. However, when we analysed the data, we found that there were differences between the two groups. The onset of jumping in the naloxone–morphine group occurred within 1·75 (±0·49) min, while a much longer time was recorded in the high

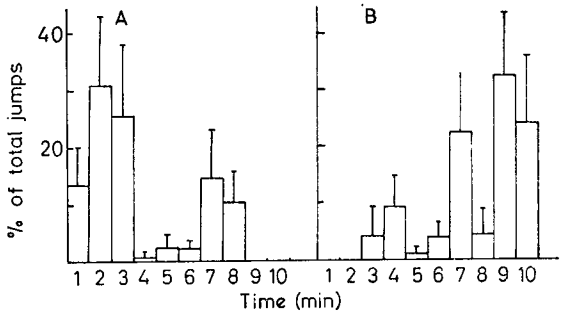

FIG. 1. The distribution of jumps in 10 minute test period. Each value represents mean ± s.e. of 8 mice. A—morphine–naloxone treated mice. B—high ambient temperature treated mice.

ambient temperature group (6·12 + 0·75 min). The number of jumps per mouse was equal in the two groups during the 10 min of the test period (23·5 ± 6·5 and 22·3 ± 5·1). During the first 2 min, more than 50% of the total number of jumps were found in the naloxone–morphine group, whereas during this time only 30% were found in animals subjected to high ambient temperature. Fig. 1 shows that during the first 3 min 70% of the total jumps were counted in the morphine–naloxone mice, while 60% were recorded during the last 3 min of the test period in the group treated with high ambient temperature.

These differences are important for estimates of the narcotic physical dependence by the jumping method. Way & others (1974) observed that high ambient temperature increases the naloxone-induced jumping in mice, but since they did not present the onset of jumping and the distribution during the test period, their results could be interpreted to mean that the high ambient temperature does not contribute to the naloxone-precipitated withdrawal syndrome. However, the increase in the last 3 min

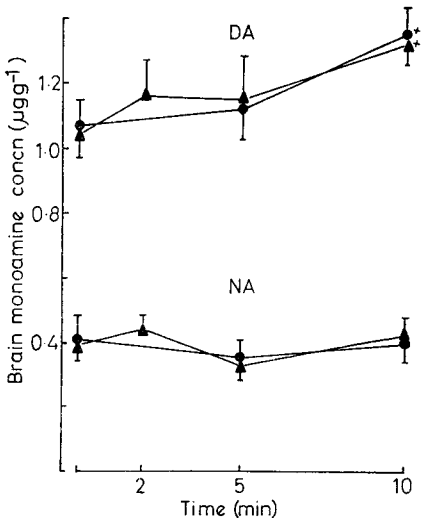

FIG. 2. The concentration of brain dopamine (DA) and noradrenaline (NA). Each value represents mean ± s.e. of 5 mice. * $P < 0.05$ with regard to 0 min value. ▲——▲ morphine-naloxone treated mice. ●——● high ambient temperature treated mice.

of the number of jumping mice indicates that this is due entirely to high ambient temperature. Therefore, it is necessary to present all the data of jumping behaviour in detail. This would also apply when other drugs able to produce jumping are used in studies of naloxone-induced jumping behaviour.

Since changes in the concentration of dopamine may relate to jumping behaviour in mice (Iwamoto & others, 1973), we measured the dopamine concentrations in the brains of experimental animals. Fig. 2 shows that the content of dopamine is significantly increased at the end of 10 min (30% over the 0 time levels) in both groups. There was no change in the concentration of noradrenaline. We also found that naloxone alone did not change the concentrations of either of the catecholamines measured. Our results indicate that the increase in dopamine concentrations occurs later than the jumping syndrome; this is in disagreement with the results of Iwamoto & others (1973), who reported the increase in dopamine concentrations occurring at the same time as jumping. The discrepancy is probably due to the fact that they used mice addicted to morphine, while we used animals after a single injection of morphine. However, in another series of experiments, in which they did not examine dopamine concentrations they found that the onset of jumping occurred 2 to 4 min after the injection of naloxone (Wei, Loh & Way, 1973), a result which is similar to ours. It seems therefore, that the increase in dopamine concentrations in the brains of jumping mice is related to the jumping behaviour in mice, similar to that observed after naloxone administered to morphine-treated rats. In summary, the onset of jumping and the distribution of jumps within the 10 min test period were different, however, in the two treatments, both of them were able to increase the dopamine concentrations within 10 min.

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