Modification of Antinociceptive Action of Morphine by Dopamine Agonist and Antagonist in Mice

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Abstract—A marked potentiation of the antinociceptive action of morphine was produced by haloperidol, but apomorphine had no effect on the antinociceptive action of morphine in acute experiments. Following chronic treatment with haloperidol, the antinociceptive action of morphine was significantly suppressed by apomorphine, and apomorphine shifted the dose-response curve of morphine to the right and increased the ED₅₀ value of morphine by 2.3-fold. These results suggest that the suppressive action of apomorphine on the antinociceptive effect of morphine in chronic haloperidol-treated mice may be due to an increased sensitivity of post-synaptic dopaminergic receptors to apomorphine.

It has been reported that the nigro-striatal dopamine (DA) system responds to a variety of noxious stimuli, e.g., tail pinch, sciatic nerve stimulation or radiant heat (1–3). Nieoullon et al. (4) reported that sensory stimulation influenced the release of DA in both the caudate nucleus and the substantia nigra. The caudate nucleus of the rat is particularly rich in opiate receptors (5–7). Jurna and Heinz (8) reported that micro-injection of morphine into the caudate nucleus produced a marked antinociceptive action, and this effect was abolished by i.p. injection of naloxone or apomorphine. These views led us to assume that the dopaminergic system is possibly involved in the regulation of the antinociceptive action of morphine. If this is the case, then the antinociceptive action of morphine should be influenced by apomorphine in animals treated chronically with haloperidol because of an increase in the sensitivity of postsynaptic dopaminergic receptors to apomorphine. The present study tested this hypothesis in an attempt to elucidate the role of the dopaminergic system in the antinociceptive action of morphine.

Male ddY-strain mice weighing between 18–22 g were used in all experiments. The animals were maintained in a constant environment with a 12 hr dark and 12 hr

light cycle. The animals had free access to food and tap water ad libitum. At least one week was allowed for acclimatization to the environment before experimentation. Antinociceptive activity was evaluated by the tail-flick method. The reaction time of the tail-flick response evoked by heat focussed to the tip of the tail was determined with a stop watch in groups of 12 mice. The usual control tail-flick latency was 2–3 sec. The peak effect of morphine in this assay occurred 30 min after administration. The doses of morphine used in the present study were 1.25, 2.5, 5.0, 10 and 20 mg/kg, i.p. The ED₅₀ values and their 95% confidence interval were determined by the method of Litchfield and Wilcoxon (9). The ED₅₀ of morphine following treatments with dopaminergic modifiers was considered significantly different from the control ED₅₀ of morphine if the experimental ED₅₀ lay outside the 95% confidence interval of the control ED₅₀ and the control ED₅₀ lay outside the 95% confidence interval of the experimental ED₅₀. Apomorphine and haloperidol were given 5 min before administration of morphine. For the chronic study, animals were administered with either 0.3% carboxymethylcellulose (CMC) (vehicle) or haloperidol (2 mg/kg, i.p.) daily for 21 consecutive days. Three days

following the last administration, these mice were administered with a test dose of morphine (1.25–20 mg/kg, s.c.). Following this, the control observation for the antinociceptive action of morphine was made in one group, and the effect of apomorphine (5 mg/kg, i.p.) on the antinociceptive action of morphine was investigated in another group. Morphine sulfate and apomorphine HCl were dissolved in saline (in the case of apomorphine, a few grains of ascorbic acid were added to the solution to prevent oxidation). Haloperidol was dissolved in 0.3% CMC. Where applicable, all drug doses were expressed as the respective salts.

In acute experiments, haloperidol (2 mg/kg, i.p.) exerted a significant enhancing action on the antinociceptive effect of morphine on the tail-flick response as shown in Fig. 1A and decreased the ED₅₀ of morphine by about 4-fold. Apomorphine (5 mg/kg, i.p.) had no influence on the antinociceptive action of morphine. Neither haloperidol (2 mg/kg) nor apomorphine (5 mg/kg) alone produced significant changes in the tail-flick response. Following chronic treatment with haloperidol, on the other hand, the antinociceptive action of morphine was significantly suppressed by apomorphine, and apomorphine (5 mg/kg, i.p.) shifted the dose-response curve of morphine to the right and increased the ED₅₀ of morphine by 2.3-fold (Fig. 1B).

In the present study, haloperidol produced a significant enhancement of the antinociceptive action of morphine in the acute experiments. Apomorphine did not show any influence on the antinociceptive action of morphine even at a high dose (5 mg/kg). Thus, it can be anticipated that physiological stimulation of DA receptors attains the maximal inhibitory effect on the antinociceptive action of morphine in mice in the normal situation, and that further stimulation of the DA receptors by apomorphine does not modify the antinociceptive action of morphine. This inhibition can be removed when the DA receptors is blocked by haloperidol, thereby resulting in a potentiation of the antinociceptive action of morphine.

In the chronic study, it was found that DA receptors stimulation by apomorphine

Fig. 1. Antinociceptive effect of morphine on the tail-flick response in mice. The columns represent the value of the ED₅₀ of morphine. A, acute experiments; B, chronic experiments. Haloperidol and apomorphine were given 5 min before administration of morphine. In the chronic experiments, three days after cessation of chronic vehicle (■) or haloperidol (□) treatment, the control response for morphine's antinociceptive action was checked. ** MOR vs. MOR+APO ($P<0.01$) in chronic haloperidol-treated mice and *** MOR vs. HAL ($P<0.001$) in acute experiments. MOR, morphine; HAL, haloperidol; APO, apomorphine.

decreased the antinociceptive effect of morphine when mice were in a state of dopaminergic supersensitivity following chronic treatment with haloperidol. The dose and length of haloperidol treatment employed in the present experiment were well established to produce a dopaminergic supersensitivity (10, 11). If the activity of dopaminergic neurons was completely suppressed due to a gradual development of a depolarization block of DA cells following chronic treatment with haloperidol (12–15), the antinociceptive action of morphine should be enhanced by the treatment. In animals treated chronically with haloperidol, however, morphine exerted

an antinociceptive action similar to that in the chronic vehicle-treated mice. It is conceivable, therefore, that some physiological activity of dopaminergic neurons after long-term treatment with haloperidol is still contributing to the inhibition of the antinociceptive action of morphine because of an increased sensitivity of the DA receptors. Further stimulation of dopamine receptors by apomorphine produced additional inhibition of the antinociceptive action of morphine, presumably due to the supersensitivity state of the dopaminergic system.

In conclusion, on the basis of the results from the present experiments, the suppressive action of apomorphine on the antinociceptive action of morphine in chronic haloperidol-treated mice, which could not be detected in acute experiments, may be due to an increased sensitivity of the postsynaptic dopamine receptors to apomorphine. This provides additional evidence to support the concept that the dopaminergic system is playing a role as an inhibitory modulator of the antinociceptive action of morphine in mice.

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