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Effect of nialamide and methyldopa on the analgesic action of morphine in rats and mice

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Methyldopa and nialamide enhance the analgesic action of morphine when administered separately in the rat. However, the association of both drugs in the same animal diminishes the effect of the analgesic. Results observed in mice differ from those found in rats, whereas methyldopa induces a slight increase in morphine analgesic effect, nialamide is ineffective. The administration of both drugs in combination increases morphine effect in a way similar to that obtained when methyldopa and morphine are administered together.

Compounds that induce a lowering of catecholamine levels in the central nervous system generally produce a decrease of the analgesic effect of morphine (Schneider, 1954; Sigg, Caprio & Schneider, 1958; Witkin, Maggio & others 1960; Medaković & Banić, 1964; Takagi, Takashima & Kimura, 1964). This antagonistic action is not shared by methyldopa. On the contrary, methyldopa induces a synergistic action when injected either a few or 24 h before the analgesic (Contreras & Tamayo, 1966; Contreras, Quijada & Tamayo, 1967). Since monoamine oxidase inhibitors cause an increase in brain monoamines, an examination of the influence of nialamide on the synergistic action of methyldopa was thought of interest.

EXPERIMENTAL

Groups of 8 adult male rats weighing between 180–230 g were employed in every experiment. Analgesia was tested by the method of Macht & Macht (1940) as modified in our laboratory (Contreras & Tamayo, 1966). Results are expressed as the mean area calculated according to Winter & Flataker (1950).

In adult male mice, weighing 25–30 g, the analgesia was assessed by the method of Woolfe & MacDonald (1944). Mice were placed on a hot plate heated at 54° ± 0·5° at 30 min intervals. The reaction time was measured from the moment the animal was placed on the plate until it reacted by licking its fore paws or by a sudden jump.

In rats the statistical significance was assessed by the *t*-test. In mice an ED50 of morphine was calculated by the usual method of probit analysis, counting as affected those animals in which post-injection reaction time exceeded the upper confidence limit (P, 0·001) of the initial reaction time. The χ^2 test was applied to the results.

Solutions in distilled water were prepared in concentrations such that each rat received a maximum of 0·4 ml/100 g. For mice the solutions were prepared for a maximum of 1 ml/100 g. All drugs were injected intraperitoneally. The drugs employed were α-methyldopa, nialamide and morphine. The scheme of their administration is described in results.

RESULTS

Effect of methyldopa and nialamide either alone or in combination on the analgesic action of morphine in rats (Table 1). The administration of methyldopa and nialamide

Table 1. *Effect of methyldopa and nialamide on the reaction threshold and on the analgesic action of morphine in rats*

Drug, mg/kg	Time before analgesic test	Area ± s.e.*
Saline		40 ± 24
Morphine, 10	30 min	480 ± 52
Methyldopa, 125	24 h	78 ± 43
Nialamide, 100	5 h	28 ± 25
Methyldopa, 125	24 h	
Nialamide, 100	5 h	65 ± 29
Methyldopa, 125	24 h	
Nialamide, 100	19 h	72 ± 26
Methyldopa, 125	24 h	
Morphine, 10	30 min	1340 ± 80†
Nialamide, 100	5 h	
Morphine, 10	30 min	744 ± 81‡
Nialamide, 100	19 h	
Morphine, 10	30 min	732 ± 98‡
Methyldopa, 125	24 h	
Nialamide, 100	5 h	
Morphine, 10	30 min	65 ± 45§
Methyldopa, 125	24 h	
Nialamide, 100	19 h	
Morphine, 10	30 min	406 ± 62§

* Analgesic effect estimated by the electrical stimulation method.
† Significantly increased from morphine alone ($P < 0{\cdot}001$).
‡ Significantly increased from morphine alone ($P < 0{\cdot}02$).
§ Significantly decreased from morphine plus methyldopa ($P < 0{\cdot}001$).

to control animals did not significantly alter the reaction threshold in rats. A synergistic action was observed in rats treated with the monoamine oxidase inhibitor or when methyldopa was administered on the morphine analgesic action. However, when both nialamide and methyldopa were administered to the same animals the effect of morphine was partially or totally counteracted. The antagonism was more evident in groups receiving the injection of nialamide 5 h before the analgesic.

Effect of methyldopa and nialamide either alone or in combination on the analgesic action of morphine in mice (Table 2). An ED50 of morphine was injected in every case. In contrast to that observed in rats, no additional analgesic activity was obtained at 30 and 60 min controls in animals treated with methyldopa, but a slight increment was observed at the 90 min control ($P < 0{\cdot}05$).

Effects induced by methyldopa on morphine analgesia did not change by the concomitant administration of nialamide. The administration of the monoamine oxidase inhibitor alone did not significantly modify the effect of the alkaloid.

Although not shown in Table 2, methyldopa (500 mg/kg) by itself increased the reaction time when measured at 4 to 6 h after its administration.

DISCUSSION

The effect of the decarboxylase inhibitor, methyldopa, on the analgesic action of morphine in rats shows some peculiarities.

The methyldopa by itself increases the reaction threshold 4 to 6 h after its administration, but if a 24 h period is allowed to elapse the reaction threshold is unaltered and the effect of morphine is markedly increased. This synergistic effect is not consistent with the fact that those drugs which produce a depletion of catecholamines also induce an antagonism of morphine analgesia. Furthermore, the antagonism by reserpine of morphine analgesia is prevented by methyldopa (Contreras & Tamayo, 1966).

Table 2. *Effect of methyldopa and nialamide on the analgesic action of morphine in mice*

Drug, mg/kg	Time before analgesic test	N*	% of mice showing analgesia Time (min) 30	60	90
Saline		60	0·0	0·0	0·0
Morphine, 3	30 min	61	49·1	34·4	4·9
Methyldopa, 125	24 h				
Morphine, 3	30 min	21	57·1	38·0	19·0†
Methyldopa, 500	24 h				
Morphine, 3	30 min	20	50·0	45·0	20·0†
Methyldopa, 500	72 h				
Morphine, 3	30 min	21	52·3	23·8	4·7
Nialamide, 100	5 h				
Morphine, 3	30 min	23	65·2	47·8	17·3
Methyldopa, 125	24 h				
Nialamide, 100	5 h				
Morphine, 3	30 min	22	54·5	50·0	31·0‡
Methyldopa, 500	24 h				
Nialamide, 100	5 h				
Morphine, 3	30 min	20§	44·4	50·0	27·7‡

* Number of mice.
† Statistically significant difference from morphine alone. $P < 0{\cdot}05$.
‡ Statistically significant difference from morphine alone $P < 0{\cdot}01$.
§ Two animals died.

The successive administration of methyldopa, nialamide and morphine also produced unexpected results. What might have been expected, at most, was a similar or greater effect than that obtained when morphine was injected after either methyldopa or nialamide alone. The possibilities that could account for the reduction of the analgesic effect could be: (a) catecholamine liberation being in part responsible for morphine analgesia, (b) the synergistic action of methyldopa being exerted through the accumulation of methylcatecholamines resulting from its biotransformation, and (c) the monoamine oxidase inhibitor opposing the liberation of methyl derivatives. This last explanation is offered only for methylcatecholamines present in the central nervous system, since nialamide in a single dose does not antagonize the action of morphine alone in rats. Nevertheless, chronic treatment with monoamine oxidase inhibitors induces a reduction of morphine effect (Timsit, 1965) which could be due to a minor liberation of catecholamines by morphine in that experimental situation.

The different mechanisms implicated in the responses to thermal stimulation by mice and electrical stimulus by rats might account for the dissimilar results observed although a different sensitivity to the drugs might also exist.

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