Effects of Amphazide (a Hydrazide of Phosphorylated Carboxylic Acids) and Tetramezine (a Diaziridine Derivative) on Central Dopaminergic Structures

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Amphazide and tetramezine, two recently synthesized compounds with antidepressant and nootropic activities, were found to have dopamine-positive activity in animals injected with apomorphine, L-Dopa, or haloperidol. Amphazide expressed this activity in most tests only when given in multiple doses, whereas tetramezine expressed it well even after a single dose.

Key Words: *amphazide; tetramezine; dopamine-positive activity*

Dopaminergic (DA) structures are involved in memory processes, promoting the recall of what was learned long ago [13,15] and, when activated, contributing to effective restoration of forgotten habits [15]. There is evidence that the DA system is implicated in mediating the effects of certain antidepressants [1,3].

The purpose of this study was to investigate how central DA structures might be influenced by two recently synthesized compounds with antidepressant and nootropic activities — amphazide, which is a hydrazide of phosphorylated carboxylic acids, and tetramezine, which is a diaziridine derivative.

MATERIALS AND METHODS

The study was conducted on 170 random-bred mice (body weight 17-22 g) and 50 random-bred rats (body weight 150-200 g).

Amphazide and tetramezine (TM) were injected intraperitoneally at 90 mg/kg body weight either once or ten times once daily, and their effects on apomorphine-induced hypothermia and stereotypy, L-Dopa-induced hypothermia and alterations in exploratory and motor activities, and haloperidol-induced catalepsy were evaluated.

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Hypothermia was produced in mice by a subcutaneous injection of apomorphine at 25 mg/kg, and their body temperature was recorded with an electric thermometer 1 and 2 h postinjection.

The total duration of sterotypy and the intensities of its components (licking, sniffing, and gnawing) were measured in rats 1 h after a subcutaneous injection of apomorphine at 20 mg/kg.

Skin temperature and exploratory and motor activities (the number of holes explored and of lines crossed in an open field) were recorded in mice 1 h after a subcutaneous injection of L-Dopa at 150 mg/kg.

The severity of catalepsy was evaluated by the ability of mice to retain an awkward posture (with the hind legs on a support 30 mm high and the forelegs on the table) for 60 sec at 10, 60, and 120 min after haloperidol injection at 5 mg/kg.

The results were statistically analyzed by Student's *t* test.

RESULTS

Amphazide potentiated the effects of apomorphine only in multiple doses, enhancing the hypothermia in mice (Fig. 1) and prolonging the stereotypy in rats (Table 1); the recording of individual stereotypy components in rats showed longer sniffing times in comparison with the control group. In contrast, TM

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potentiated the hypothermic effect of apomorphine in both dosing schedules (Fig. 1) and shortened the duration of apomorphne-induced stereotypy in rats when administered once, but prolonged it when given in multiple doses (Table 1); sniffing and gnawing in the stereotypic movements of animals were expressed to equal degrees.

Amphazide weakened the L-Dopa-induced hypothermia and inhibition of exploratory and motor activities in mice after multiple injections and did not modify these effects of L-Dopa appreciably after a single injection, whereas TM markedly potentiated the L-Dopa effects in mice on both dosing schedules (Fig. 2 and Table 2) and, in addition, induced stereotypic movements in mice on the multiple dose schedule.

Both amphazide and TM in single as well as multiple doses mitigated the catalepsy induced by haloperidol in mice (Fig. 3); moreover, no signs of catalepsy were observed after haloperidol in some mice given TM. These mice were excluded from the statistical analysis, which explains why some of the differences between the control and test groups are insignificant.

Thus, the impact of amphazide (a hydrazide of phosphorylated carboxylic acids) and TM (a diaziridine derivative) on the DA system was assessed in this study by evaluating their interactions with apomorphine, L-Dopa, and haloperidol, each of which acts on DA structures in its own way. Both amphazide and TM proved to exhibit dopamine-positive activity with respect to each of these three substances.

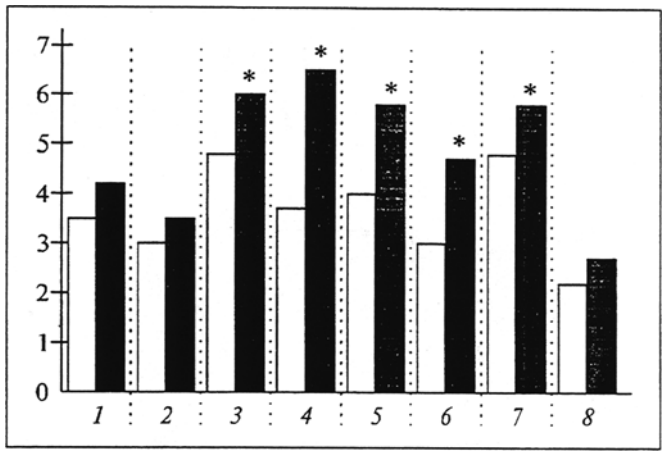

Fig. 1. Effects of amphazide and tetramezine (TM) on apomorphine-induced hypothermia in mice. Ordinate: falls of body temperature (degrees) at 60 min (*1*, *3*, *5*, and *7*) and 120 min (*2*, *4*, *6*, *8*) after apomorphine injection. White bars: control mice (those given apomorphine alone); black bars: mice given a single (*1* and *2*) or multiple (*3* and *4*) amphazide doses+apomorphine or a single (*5* and *6*) or multiple (*7* and *8*) TM doses +apomorphine. Here and in Figs. 2 and 3: the asterisk denotes a significant difference from the control group.

The cataleptic effect of neuroleptics such as haloperidol has been associated with their ability to block DA receptors, accelerate dopamine turnover, and raise the levels of dopamine metabolites [12]. L-Dopa mainly acts by raising dopamine levels in the brain [8], which is believed to account for its influ-

TABLE 1. Effects of Amphazide and Tetramezine (TM) on the Duration of Apomorphine-Induced Stereotypy in Rats ($M \pm m$) Group

Group	Duration of stereotypy after apomorphine injection, min	
	single dose	multiple doses
Control (apomorphine alone)	96.6±1.8	62.3±4.7
Apomorphine+TM	83.6±2.4*	134.5±7.8*
Control (apomorphine alone)	80.2±4.9	80.2±4.9
Apomorphine+amphazide	61.2±2.5	130.7±6.1*

Note. *$p<0.05$ in comparison with the control group.

TABLE 2. Effects of Amphazide and Tetramezine (TM) on L-Dopa-Induced Inhibition of Exploratory and Motor Activities

Group	Exploratory and motor activities	
	No. of holes explored	No. of lines crossed
Intact	27±1.5	31±1.5
Control (L-Dopa alone)	6±0.5*	7±1.5*
L-Dopa+TM (single dose)	3±1.2**	3±0.9**
L-Dopa+TM (multiple doses)	14±3.2**	30±9.8**
L-Dopa+amphazide (single dose)	6±0.8	10±1.4
L-Dopa+amphazide (multiple doses)	12±1.6**	24±2.4**

Note. *$p<0.05$ in comparison with the intact group; **$p<0.05$ in comparison with the control group.

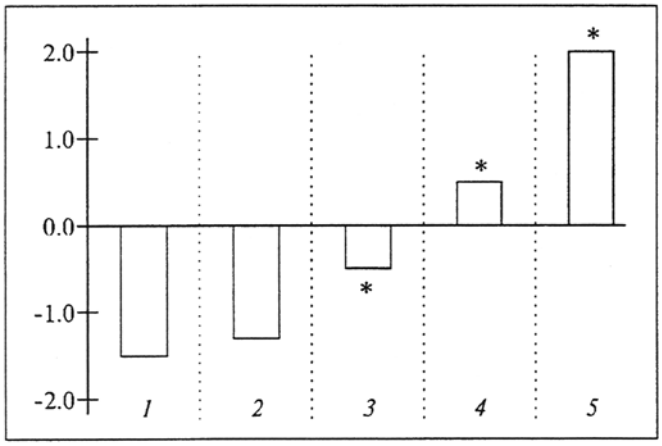

Fig. 2. Effects of amphazide and tetramezine (TM) on L–Dopa–induced hypothermia in mice. Ordinate: changes in body temperature (degrees) caused by L–Dopa; *1*) control mice (those given L–Dopa alone); *2–5*) mice given a single (*2*) or multiple (*3*) amphazide doses + L–Dopa or a single (*4*) or multiple (*5*) TM doses + L–Dopa.

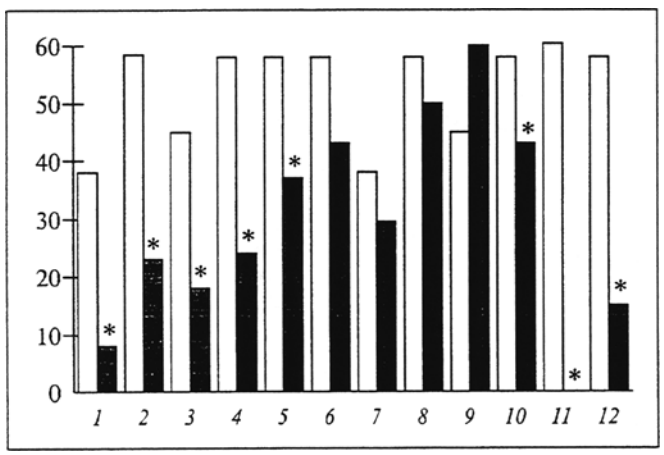

Fig. 3. Effects of amphazide and tetramezine (TM) on the duration of haloperidol–induced catalepsy in mice. Ordinate: duration of catalepsy (seconds) 10 min (*1*, *4*, *7*, and *10*), 60 min (*2*, *5*, *8*, and *11*), and 120 min (*3*, *6*, *9*, and *12*) after haloperidol injection. White bars: control mice (those given haloperidol alone); black bars: mice given a single (*1–3*) or multiple (*4–6*) amphazide doses + haloperidol or a single (*7–9*) or multiple (*10–12*) TM doses + haloperidol.

ence on motor activity among other effects [11]. Apomorphine effects such as stereotypy and hypothermia have been ascribed, in the main, to stimulation of DA receptors [10].

Amphazide effects were detected in most tests only after multiple doses, whereas TM was, as a rule, also effective after a single dose. This suggests that TM may act directly on unchanged DA receptors, but that some reorganization of these receptors is required before they can be acted upon effectively by amphazide. Also, amphazide and TM exerted unequal effects on individual components of apomorphine-induced stereotypy. Stereotypic movements of rats given apomorphine after prolonged treatment with amphazide were dominated by sniffing, which is mediated via the mesolimbic system [4], whereas in rats given apomorphine after TM, sniffing movements were expressed to the same degree as those of gnawing, which is mediated via the nigrostriatal system [4]. The mesolimbic DA system plays an important role in orchestrating adaptive behavior under stress [2,5] and in learning and memory processes [2,14]. Evidence for the involvement of mesolimbic DA structures in mediating the effects of antidepressants has also been reported [6,7].

The mechanism(s) by which amphazide and TM interact with DA structures requires further study. Both compounds contain an amino group, which is free in amphazide and closed in a three-membered ring in TM. DA receptors are known to have nonspecific binding sites for the nitrogen of the amino group [9], and the differential pharmacological effects of amphazide and TM might therefore be due to differences in the position of the amino group nitrogen in these compounds.

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