RESEARCH PAPERS

THE HYPOTHERMIC AND SEDATIVE ACTION OF RESERPINE IN THE MOUSE

BY A. W. LESSIN AND M. W. PARKES

From the Biological Laboratories, Research Department, Roche Products Limited, Welwyn Garden City

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The sedative action of reserpine has been studied by its effects upon the body temperature of the mouse, in comparison with chlorpromazine and 5-hydroxytryptamine (5-HT). Reserpine and chlorpromazine produce hypothermia and sedation in the mouse by interference with the mechanism of temperature regulation, but 5-HT acts in a different manner. The central stimulants, lysergic acid diethylamide, amphetamine and tetrahydro-β-naphthylamine, antagonised the hypothermic effects of reserpine, chlorpromazine and 5-HT. Iproniazid antagonised the hypothermic effects of reserpine, while potentiating those of chlorpromazine and 5-HT. This evidence does not seem to support the hypothesis that the sedative action of reserpine is mediated by 5-HT.

IT has been shown that reserpine causes the disappearance of 5-hydroxytryptamine (5-HT) from various tissues[1–8]. Brodie and his colleagues have consequently suggested that the sedative actions of reserpine are mediated by released 5-HT[9]. In support of this hypothesis they have put forward the evidence that both reserpine and 5-HT have sedative actions in the mouse and can be antagonised by lysergic acid diethylamide (LSD)[10,11].

We have already shown[12] that reserpine, chlorpromazine and 5-HT all lower body temperature in the mouse. Moreover, it was shown for the first two agents that this hypothermic effect may be used as a measure of sedative action. We have further examined the properties of all three agents to determine the extent to which resemblances between the actions of reserpine and 5-HT support Brodie's hypothesis.

METHODS

Rectal temperatures were measured in mice as previously described[12]. Groups of 5 mice had mean temperatures recorded. Except where otherwise stated the room temperature was 22°. All drugs were injected intraperitoneally, in a volume of 0·2 ml./20 g. mouse; they were dissolved in water or saline with the exception of reserpine, which was dissolved in 2N acetic acid, neutralised as far as possible and diluted with water.

RESULTS

Sedative Effects

The first visible sign after injection of moderate doses of reserpine in the mouse is ptosis of the eyelids and this occurs after 10 to 20 minutes. After 30 to 120 minutes sedation commences and body temperature falls,

the mice presenting a characteristic hunched attitude with piloerection, and crowding together in a corner. When handled, they respond normally but become inactive after a short interval. As the body temperature continues to fall the response to handling becomes weaker, although it never completely disappears. Six hours after doses of 3 mg./kg. or more the mice have temperatures approaching that of the room and may be placed on their sides, although attempts to rise are eventually successful.

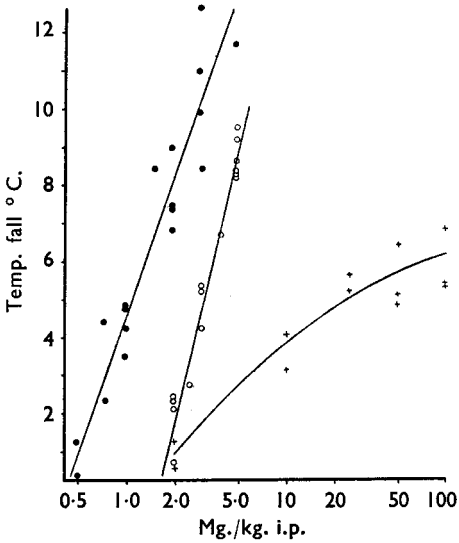

FIG. 1. The effect of chlorpromazine, reserpine and 5-hydroxytryptamine upon the rectal temperature of mice. Each value for temperature fall is the lowest recorded for a group of 5 mice after injection of the drug, and is expressed as the difference from the mean value for an untreated group.

● Reserpine; $b = 12{\cdot}0 \pm 1{\cdot}9$ ($P = 0{\cdot}95$)
○ Chlorpromazine; $b = 17{\cdot}8 \pm 2{\cdot}2$ ($P = 0{\cdot}95$)
+ 5-HT.

By contrast, the fall in temperature with chlorpromazine is immediate, and the predominant feature is muscular weakness, the mice lying outstretched and making no attempts to crowd together. Responses to handling are typically reduced and with doses above 5 mg./kg. the mice barely respond and are unable to resume an upright position when placed on their sides, although they make feeble efforts to do so.

The fall in temperature with 5-HT is also immediate and the mice appear characteristically limp. The appearance of mice sedated with any of these three agents allows them to be readily distinguished.

The maximum fall in rectal temperature was determined for several doses of reserpine, chlorpromazine and 5-HT. As we have shown[12], this occurs at about 6 hours after injection with reserpine and between 1 and 3 hours with chlorpromazine, depending upon dose. With 5-HT, maximum effect occurs after 20 minutes to 1 hour, again depending on dose. Figure 1 shows that a regression of maximum temperature fall with dose occurs for each substance, although with 5-HT the regression on log dose did not appear to be linear over the whole range.

The delay in onset of hypothermia after intravenous injection of up to 2 mg./kg. reserpine in mice was found to be similar to that observed after intraperitoneal injections. This is in agreement with the delay in onset of other effects of reserpine administered by various routes[13]. A very large dose (20 mg./kg. i.p.), however, produced an immediate effect, the temperature falling 4°, within 30 minutes. It was also found that a more rapid fall was produced by small doses when the mice were

kept at room temperatures below 22° and the extent of the fall was greater than at higher room temperatures.

Effect of External Temperature

As we have already shown, no hypothermia occurs in mice with reserpine or chlorpromazine at an ambient temperature of 32°[12]. On the other hand, 50 mg./kg. 5-HT lowered body temperature under these conditions, the mice being limp and sedated. At 38–40°, reserpine and

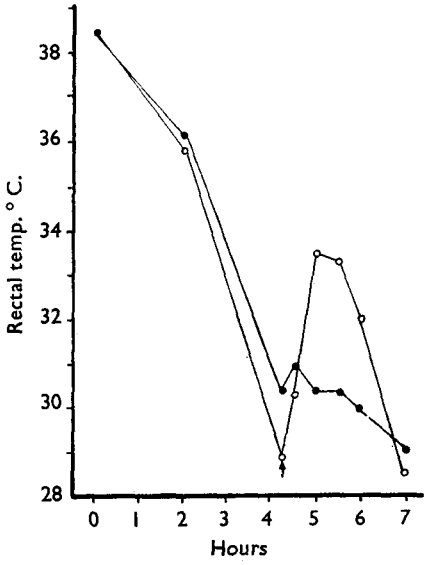

FIG. 2. The effect of LSD on the hypothermic action of reserpine.
●——● Reserpine, 2 mg./kg. i.p. (At arrow—water 0·15 ml./20 g. i.p. given 4¼ hr. later.) ○——○ Reserpine, 2 mg./kg. i.p. (At arrow —0·75 mg./kg. LSD in 0·15 ml./20 g. i.p. given 4¼ hr. later.)

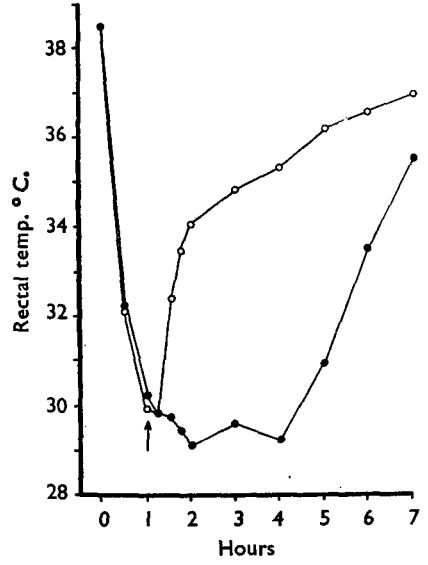

FIG. 3. The effect of LSD on the hypothermic action of chlorpromazine.
●——● Chlorpromazine 5 mg./kg. i.p. (At arrow—water 0·15 ml./20 g. i.p. given 1 hr. later.)
○——○ Chlorpromazine 5 mg./kg. i.p. (At arrow—0·75 mg./kg. LSD in 0·15 ml./20 g. i.p. given 1 hr. later.)

chlorpromazine caused a rise in the rectal temperature of mice, an effect similar to that previously reported for reserpine in other species[14]. At this temperature reserpine still caused ptosis of the eyelids but no appreciable sedation, while chlorpromazine produced excitement, as reported by Berti and Cima[15]. Mice given reserpine and kept at an ambient temperature of 32° for periods up to 4 hours showed no sedation, but their temperature fell and they became sedated immediately on removal to a room temperature of 22°.

Effects of LSD, Amphetamine and Tetrahydro-β-naphthylamine

The hyperthermic action of amphetamine was readily confirmed in mice, but LSD, which raises body temperature in rabbits[16] produced only a slight fall in mice in doses from 0·25 to 10 mg./kg., after a short

period of motor stimulation. However, a rise in temperature was produced by 5 mg./kg. LSD in mice kept at 32°. Similar results were obtained with tetrahydro-β-naphthylamine (50 mg./kg.) and it is concluded that stimulants do not readily raise the body temperature of mice at 22°, but are able to do so at thermal neutrality. LSD given 4 hours after reserpine, 1 hour after chlorpromazine or 30 minutes before 5-HT, clearly antagonised the hypothermic effects of all three agents (Figs. 2, 3 and 4). In each case, signs of sedation were also visibly reduced; it was noticeable that ptosis of the eyelids caused by reserpine was also abolished. The antagonism of LSD towards reserpine lasted about an hour, body temperatures subsequently falling to the level of the control group, whereas with chlorpromazine and 5-HT this subsequent fall did not occur. Similar antagonism of the effects of reserpine and chlorpromazine was observed with 50 mg./kg. tetrahydro-β-naphthylamine and 10 mg./kg. amphetamine.

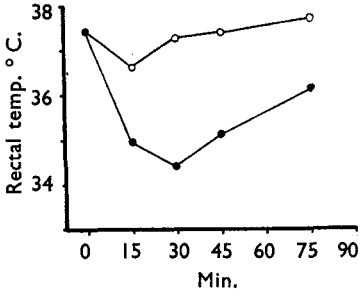

FIG. 4. The effect of LSD on the hypothermic action of 5-HT.
●——● 5-HT 20 mg./kg. i.p.
○——○ 5-HT 20 mg./kg. i.p. 30 min. after LSD 0·75 mg./kg.

Effect of Enzyme Inhibitors

Iproniazid has been reported to antagonise sedation due to reserpine in the rabbit[17] and in the mouse[18,19]. We have observed a corresponding antagonism towards effects on the body temperature of the mouse, hypothermia and sedation being completely prevented by 100 mg./kg. iproniazid, given to mice 24 hours before reserpine[20]. Iproniazid, given before chlorpromazine or 5-HT potentiated their hypothermic effects (Figs. 5, 6).

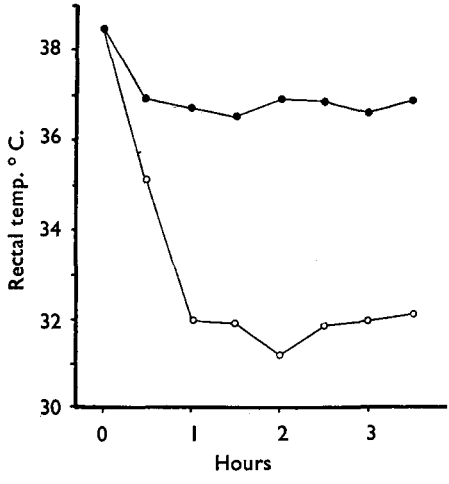

FIG. 5. The effect of iproniazid on the hypothermic action of chlorpromazine.
●——● Chlorpromazine 3 mg./kg. i.p.
○——○ Chlorpromazine 3 mg./kg. i.p. 1½ hr. after iproniazid 100 mg./kg. i.p.

Iproniazid is not only a powerful inhibitor of monoamine oxidase, but has been shown to inhibit the enzyme present in liver microsomes which plays a part in barbiturate detoxication[21]. In this respect it resembles the inhibitor SKF 525A[22] and it was therefore of interest to determine the effects of this inhibitor on the hypothermic agents. Table I summarises the results obtained with both inhibitors, and Figure 7

illustrates the strong potentiation of the effect of chlorpromazine by SKF 525A. The effect of SKF 525A upon reserpine was less marked, while 5-HT was unaffected. Neither iproniazid nor SKF 525A affected body temperature in the doses used.

TABLE I

EFFECTS OF ENZYME INHIBITORS UPON HYPOTHERMIA CAUSED BY RESERPINE, CHLORPROMAZINE AND 5-HYDROXYTRYPTAMINE

Enzyme Inhibitor	Effect upon hypothermia by		
	Reserpine	Chlorpromazine	5-HT
Iproniazid	Antagonism	Potentiation	Potentiation
SKF 525A	Potentiation	Potentiation	No effect

DISCUSSION

Although there is a superficial resemblance between the effects of injections of reserpine and 5-HT in the mouse, in that both lower body temperature and produce sedation, we have shown that a number of differences exist. The effects of reserpine appear to be exerted upon thermoregulation, since at thermoneutrality, the temperature at which heat loss is at a minimum, neither hypothermia nor sedation are produced[12], while at ambient temperatures above 37° hyperthermia occurs. With 5-HT, on the other hand, both temperature fall and sedation occur at thermoneutrality, implying either a fall in heat production or an increase in heat loss. It is possible that this action is largely a peripheral one.

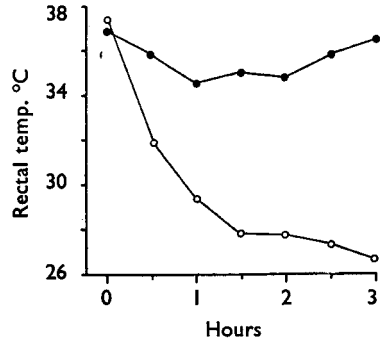

FIG. 6. The effect of iproniazid on the hypothermic action of 5-HT.
●——● 5-HT 25 mg./kg. i.p.
○——○ 5-HT 25 mg./kg. i.p. 1½ hr. after iproniazid 100 mg./kg. i.p.

Although we have confirmed that the 5-HT antagonist, LSD, reduces the sedative action of reserpine and 5-HT, as measured by its antagonism towards the hypothermia caused by these agents, it is significant that the hypothermia of chlorpromazine was also antagonised in the same way. Moreover, amphetamine and tetrahydro-β-naphthylamine were also effective in antagonising the hypothermic effect of reserpine, chlorpromazine and 5-HT.

We conclude, therefore, that the antagonism of LSD towards reserpine and 5-HT is not specific, but may be due to its stimulant action, which it exerts in common with amphetamine and tetrahydro-β-naphthylamine. There is thus no reason to regard this antagonism as related to the antiserotonin properties of LSD. A similar conclusion concerning the central actions of LSD was reached by Gaddum and Vogt[23] from their studies of intraventricular injections.

The similarities between the sedative properties of reserpine and 5-HT, which were considered by Brodie and colleagues[3] to support the hypothesis that reserpine action is mediated by 5-HT, have been shown to extend to chlorpromazine also. Moreover, reserpine and 5-HT differ in certain important respects; their mode of action appears to be different, and iproniazid, which antagonises the action of reserpine, potentiates that of 5-HT. With reserpine there is a fall in the 5-HT content of the brain[24], the maximum sedative effect of the drug occurring when brain 5-HT is at its lowest level. The prevention of reserpine sedation by iproniazid is associated with retention of brain 5-HT[24] and this has been related to the amount of inhibition of monoamine oxidase in the brain[20]. Thus, if brain 5-HT is concerned in reserpine sedation it is more likely that the effect is due to a deficiency in 5-HT than to mediation by the amine.

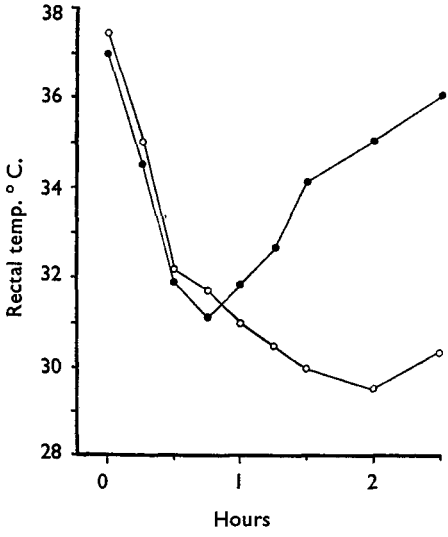

Fig. 7. The effect of SKF 525A on the hypothermic action of chlorpromazine.

●——● Chlorpromazine, 2 mg./kg. i.p.

○——○ Chlorpromazine, 2 mg./kg. i.p. 40 min. after SKF 525A, 10 mg./kg. i.p.

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