Effect of reserpine on the histaminolytic activity of guinea-pig liver

SIR,—Sachdev, Aiman & Rajapurkar (1961) showed that serpentine, but not reserpine, inhibited histaminase. Serpentine was shown to potentiate the response of guinea-pig ileum, uterus and trachea to histamine in doses similar to that of aminoguanidine used by Arunlakshana, Mongar & Schild (1954). It also inhibited the action of a preparation of histaminase (Torantil).

Gaitonde, Satoskar & Mandrekar (1960) showed that injection of 10 μg of reserpine into the lateral ventricle of cats produced an inhibition of gastric acidity, while intravenously 50 μg reserpine increased gastric acidity as well as blood histamine levels. Gaitonde & Shaligram (1960) administered 500 μg of reserpine intravenously in cats under chloralose anaesthesia and showed an increase in gastric acidity from 1·06 m-equiv. to 2·77 m-equiv. (213%). The blood histamine was increased from 0·053 μg/ml to 0·183 μg/ml. Sachdev, Dave & Panjwani (1965) found that urine of guinea-pig and man given reserpine, potentiated the response of the guinea-pig ileum to histamine. Suspecting antihistaminase activity in some metabolite produced during reserpine therapy, they found that methyl reserpate, a well known metabolite of reserpine, produced a moderate inhibition of the histaminolytic activity of guinea-pig liver. The effect of reserpine administration in the usual therapeutic doses on the histaminolytic activity of guinea-pig liver has therefore been examined.

Three groups of 3 adult guinea-pigs each were fed with 0·1 mg/kg reserpine daily, for 1, 2 and 3 weeks respectively. One group was kept as a control. 3 more animals were fed with 1, 5 and 10 mg/kg of aminoguanidine respectively, for 3 days. Histaminolytic activity was estimated in the supernatant of a homogenised and centrifuged preparation of liver, taken immediately after death (Spencer, 1963). A known amount of histamine was added and the preparation incubated in a Warburg apparatus at 37°. The histamine content of the incubates at 0, 10, 20, 40, 80 min was assayed, after boiling, on the ileum of guinea-pig treated with atropine.

The time in which 50% histamine was destroyed (DT50) was calculated from the graph obtained. The average DT50 in the 3 control animals was 41 min, s.d. $\pm$ 11. This was reduced to 24 min $\pm$4 after one week of administration of reserpine, indicating an increased histaminolytic activity. However the difference was statistically insignificant. The average DT50 after 2 and 3 weeks administration of reserpine was 58 $\pm$ 14 and 76 $\pm$ 10 respectively. The number of animals in each group was too small to permit a reliable estimate of change in histaminolytic activity until after 3 week treatment when a statistically significant decrease was observed $t = 3{\cdot}948$; $P = 0{\cdot}05$. Aminoguanidine, 5 and 10 mg/kg depressed the activity significantly, but 1 mg/kg did not produce any effect.

The slight initial increase in the histaminolytic activity may have been due to adaptive induction of the enzyme by histamine or by some metabolite of reserpine. Southren, Kobayashi, Levine & Sherman (1965) have, however, shown that subcutaneous administration of 0·3 to 1·2 mg of histamine daily for 45–48 days, in women, did not affect the plasma diamine oxidase levels.

Inhibition of the histaminolytic activity of liver during reserpine administration may explain hyperchlorhydria induced by reserpine. Six cats were anaesthetised with 80 mg/kg of chloralose and given 0·25 to 0·5 mg/kg of reserpine intravenously or 0·25 to 2 mg/kg methyl reserpate; this treatment induced a prolonged increase in gastric secretion and acidity. Reserpine was more powerful and produced a 3 to 4 times increase which lasted for 4–5 hr.

Prior administration of SKF 525–A markedly inhibited the hyperchlorhydria produced by reserpine, indicating that hyperchlorhydria was probably due to a metabolite.

Efforts to isolate from the urine of animals treated with reserpine the metabolite responsible for potentiating the histamine response, have so far been unsuccessful.

Department of Pharmacology,
M.P. Shah Medical College,
Jamnagar, India.
February 15, 1966

B. P. UDWADIA
K. S. SACHDEV
D. J. JOSHI

References

Arunlakshana, O., Mongar, J. L. & Schild, H. O. (1954). *J. Physiol., Lond.*, **123**, 32–54.
Gaitonde, B. B., Satoskar, R. S. & Mandrekar, S. S. (1960). *Archs int. Pharmacodyn. Thér.*, **127**, 118–127.
Gaitonde, B. B. & Shaligram, S. V. (1960). *Indian J. Physiol. Pharmac.*, **4**, 249–256.
Sachdev, K. S., Aiman, R. & Rajapurkar, M. V. (1961). *Br. J. Pharmac. Chemother.*, **16**, 146–152.
Sachdev, K. S., Dave, K. C. & Panjwani, M. H. (1965). *Archs int. Pharmacodyn. Thér.*, **157**, 14–20.
Southren, A. L., Kobayashi, Y., Levine, L. & Sherman, D. H. (1965). *Am. J. Obstet. Gynec.*, **92**, 207–210.
Spencer, P. S. J. (1963). *J. Pharm. Pharmac.*, **15**, 225–232.

In vivo inhibition of ^{3}H-noradrenaline uptake by mouse brain slices *in vitro*

SIR,—Pretreatment of animals with reserpine decreases the capacity of tissues to accumulate tritiated noradrenaline *in vitro* (Dengler, Spiegel & Titus, 1961a; Ross & Renyi, 1966). Several other psychoactive compounds added to brain slices *in vitro* are known to inhibit the uptake of noradrenaline (Dengler, Spiegel & Titus, 1961b). However, pretreatment of mice with these compounds does not seem to decrease the noradrenaline uptake by subsequently prepared brain slices. In contrast to reserpine, most of these compounds seem to act reversibly and are probably loosely bound to the tissues. The tissue contents of these substances may therefore decrease during the *in vitro* incubation procedure by diffusion of the compounds into the incubation medium. We have tried to avoid this diffusion by using a briefer incubation period than was used in the aerlier experiments.

Mice were injected intraperitoneally with the compounds and they were killed at the time noted in Table 1. The incubation of the brain cortex slices with the tritiated noradrenaline and the extraction of the amine taken up was as previously described (Ross & Renyi, 1964), with the exception that the incubation time was only 5 min. Four animals were used for each compound. The content of the amine in the slices was expressed as nmol/g. The statistical significance was calculated according to the Student's *t*-test.

The results obtained are presented in Table 1. Compounds supposed to inhibit the noradrenaline uptake at the cell membrane level (Carlsson & Waldeck, 1965), namely, desipramine, imipramine or amitriptyline, were strong inhibitors of the uptake of tritiated noradrenaline under the conditions used. But cocaine, which when added *in vitro* is a powerful inhibitor of the noradrenaline uptake by brain slices, had only a slight effect when injected *in vivo*. This finding would seem to suggest that too small amounts of cocaine reach the mouse brain *in vivo*.

The large dose of chlorpromazine strongly inhibited the noradrenaline uptake, but the smaller dose had no effect although the animals were strongly tranquillised. This result may indicate that the phenothiazine class of tranquillisers