endogenous 5-HT and NA was similar to that described before on the exogenous amines (Reimers et al 1976; Peyer & Pletscher 1981).

The present finding that most of the endogenous NA like the 5-HT is releasable by thrombin indicates a preferential localization of endogenous NA in the granular pool of human platelets. Therefore, when the release reaction occurs in vivo, e.g. in the course of platelet aggregation, NA is likely to be liberated together with 5-HT. Although the absolute amounts of liberated NA can only be very small (NA-content in our experiments: $4{\cdot}67 \pm 0{\cdot}75$ pmol/10^9 platelets), some local action of this amine (released, for instance, from platelet clots in microvessels) cannot be excluded. This would be especially the case when the platelets contain elevated amounts of NA, as in situations of stress (Da Prada & Picotti 1979). A further factor to be considered is that the released NA unlike 5-HT cannot be inactivated by reuptake into the platelets.

The author thanks Miss Fabrizia Ferracin and Miss Brigitte Gieux for skilful technical assistance.

REFERENCES

Da Prada, M., Picotti, G. B. (1979) Br. J. Pharmacol. 65: 653–662

Da Prada, M., Zürcher, G. (1976) Life Sci. 19: 1161–1174

Da Prada, M., Tranzer, J. P., Pletscher, A. (1972) Experientia 28: 1328–1329

Graf, M., Laubscher, A., Richards, J. G., Pletscher, A. (1979) J. Lab. Clin. Med. 93: 257–265

Peyer, M., Pletscher, A. (1981) Naunyn-Schmiedeberg's Arch. Pharmacol. 316: 81–86

Pletscher, A. (1978) in: Youdim, M. B. H. (ed.) Essays in neurochemistry and neuropharmacology, vol. 3. John Wiley & Sons, Ltd., London, pp 49–101

Reimers, H. J., Kinlough-Rathbone, R. L., Cazenave, J.-P., Senyi, A. F., Hirsch, J., Packham, M. A., Mustard, J. F. (1976) Thromb. Haemostas. 35: 151–166

Shellenberger, M. K., Gordon, J. H. (1971) Anal. Biochem. 39: 356–372

J. Pharm. Pharmacol. 1981, 33: 670–671
Communicated February 16, 1981

0022–3573/81/100670–02 $02.50/0
© 1981 J. Pharm. Pharmacol.

Effect of trazodone, mianserin, iprindole and zimelidine on wet dog shakes produced by carbachol in rats

L. Turski*, S. J. Czuczwar, W. Turski, Z. Kleinrok, *Department of Pharmacology Institute of Clinical Pathology, Medical School, Jaczewskiego 8, PL 20–090 Lublin, Poland*

Intracerebroventricular administration of a potent cholinomimetic agent, carbachol chloride, produced wet dog shakes in rats (Turski et al 1981a). Evidence derived from our behavioural and biochemical studies, suggests that this effect may be interpreted in terms of the unique imbalance, between the central cholinergic and noradrenergic activity (unpublished data) and it seems to be independent of 5-hydroxytryptaminergic functions (Turski et al 1981b). Recently, we have reported that the shaking behaviour apparently responds to treatment with tricyclic antidepressants and monoamine oxidase inhibitors (Turski et al 1981c). Thus, the question arises of the possible use of carbachol-induced behavioural responses as an animal model sensitive to antidepressant treatment. Trazodone, mianserin, iprindole and zimelidine have been found to be effective in the treatment of depression (Daneman 1967; Brogden et al 1978; Ayd 1979; Montgomery 1980), although their mechanism of action still remains unclear. Although these drugs differed widely in their profiles of action, we attempted to study their influence on carbachol-induced wet dog shakes.

Male Wistar rats (180–210 g) were treated with intraperitoneal injections of 0·9% NaCl (saline), trazodone . HCl (2·5, 5, 10, 20 mg kg^{-1}; Francesco Angelini, Rome, Italy), mianserin HCl (5, 10, 15, 20 mg kg^{-1}; Organon, West Orange, N.J., U.S.A.), iprindole HCl (1, 2, 4, 8 mg kg^{-1}; Wyeth, Windsor, Ontario, Canada) or zimelidine HCl (2·5, 5, 10, 20 mg kg^{-1}; Astram Södertälje, Sweden), all antidepressants being administered in saline 0·5 ml/100 g 1 h before intracerebroventricular (i.c.v.) administration of carbachol chloride (OY Star AB, Tampere, Finland: 10 μg), dissolved in 10 μl sterile buffered saline, pH = 7·35 according to Herman (1970).

* Correspondence.

Eight rats, assigned to all experiments by means of a completely randomized schedule, were put into individual Plexiglas cages (25 × 15 × 10 cm) placed in a well-lighted and quiet room maintained at 21 ° ± 1 °C. Wet dog shakes were counted immediately after i.c.v. carbachol chloride over a duration of 60 min. Saline-injected i.p. or i.c.v. rats served as respective controls. The data collected from behavioural experiments were treated by means of Student's *t*-test.

Fig. 1 shows the effect of drugs on carbachol-induced wet dog shakes. Trazodone dose-dependently antagonized the response while mianserin induced a statistically significant reduction only at the dose of 20 mg kg^{-1}. Significant potency against the behaviour was displayed by iprindole while zimelidine (20 mg kg^{-1}) only slightly modified it. The numbers of wet dog shakes in the control rats were less than 1 during the 60 min.

There is no evidence so far that trazodone, mianserin, zimelidine or iprindole may have potent anti-acetylcholine activity (Leonard 1980), so the efficacy of these drugs against carbachol-induced wet dog shakes cannot be ascribed to the blockade of central muscarinic cholinergic receptors. The anti-5-HT properties of trazodone and

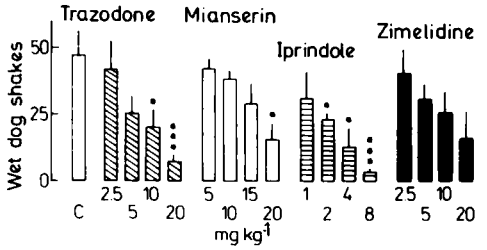

FIG. 1. Effect of trazodone, mianserin, iprindole and zimelidine on wet dog shake response produced by carbachol chloride (10 μg/rat i.c.v. in rats). All drugs were administered i.p. 1 h before carbachol. Wet dog shakes were counted over a duration of 60 min. Each value represents mean with s.d. of 8 animals. C – carbachol-injected control group, * $P < 0.05$; *** $P < 0.01$ when compared with the carbachol-injected control group.

mianserin also appear to play a minor role in the inhibitory effects of both drugs, owing to superimposed potent 5-HT uptake blocking action. Alternatively, the stimulation of central 5-HT-ergic structures achieved with zimelidine (Ross et al 1976; Buus-Lassen 1978) not only failed to potentiate the wet dog shake response but the large doses attenuated it. Thus, the inhibitory effects of trazodone, mianserin and iprindole seem to be tentatively explained in terms of the enhancement of noradrenergic transmision. In fact, both mianserin (Tang & Seeman 1980) and trazodone (Clements-Jewery et al 1980) effectively block α_2-adrenoceptors resulting in an increase of noradrenaline release and may finally produce an enhancement of noradrenaline responses at α_1-adrenoceptors. Furthermore, mianserin has been found to be a weak inhibitor of noradrenaline reuptake (Goodlet et al 1977) and trazodone can enhance the K^+-stimulated efflux of [^{3}H]noradrenaline from rat occipital cortex (Clements-Jewery et al 1980). Iprindole has no inhibitory activity on noradrenaline uptake and does not interact with α_2-adrenergic and 5-HT-ergic binding sites but enhances the spontaneous and K^+-stimulated efflux of noradrenaline from rat brain slices (Hendley 1978). The involvement of brain noradrenergic functions in the inhibition of wet dog shakes has been well documented (Turski et al 1981a). For instance, a 6-hydroxydopamine-induced selective depletion of brain noradrenaline resulted in a dramatic increase in the number of wet dog shakes and i.c.v. administered noradrenaline blocked the shaking response (unpublished data). Moreover, clonidine, which on one hand decreases the availability of noradrenaline at α_1-adrenoceptors via the stimulation of α_2-adrenoceptors (Langer 1977), and on the other, directly stimulates α_1-adrenoceptors (Andén et al 1970), distinctly inhibited wet dog shake behaviour (Turski et al 1981a). Zimelidine which has been shown to be more selective than clomipramine in inhibiting 5-HT uptake (Ross et al 1976) slightly decreases carbachol-induced wet dog shakes. This effect may support the hypothesis that the carbachol-induced shaking response is not necessarily related to the increased 5-HT-ergic transmission (Turski et al 1981b). It is apparent from our previous experiments that 5-hydroxytryptophan and clomipramine are capable of altering carbachol-induced shaking behaviour (Turski et al 1981a). However, caution is needed in assuming that a direct connection exists between the inhibition of wet dog shakes and distinct potentiation of 5-HT-ergic transmission.

In conclusion, it is suggested that the inhibitory action of trazodone, mianserin and iprindole against wet dog shakes may be explained on the basis of enhanced noradrenergic transmission. The inhibitory action of zimelidine is more complex.

REFERENCES

Andén, N.-E., Corrodi, H., Fuxe, K., Hökfelt, T., Rydin, C., Swensson, T. (1970) Life Sci. 9: 513–523

Ayd, F. J. (1979) Int. Drug Ther. Newslett. 14: 9–10

Brogden, R. N., Heel, R. C., Speight, T. N., Avery, G. S. (1978) Drugs 16: 273–301

Buus-Lassen, J. (1978) Eur. J. Pharmacol. 47: 351–358

Clements-Jewery, S., Robson, P. A., Chidley, L. J. (1980) Neuropharmacology 19: 1165–1173

Daneman, E. A. (1967) Psychosomatics 9: 208–214

Goodlet, I., Mirevlees, S. E., Sugrue, M. F. (1977) Br. J. Pharmacol. 61: 307–313

Hendley, E. D. (1978) Neurosci. Abs. 4: 494

Herman, Z. S. (1970) Psychopharmacologia Berl. 16: 369–374

Langer, S. Z. (1977) Br. J. Pharmacol. 60: 481–497

Leonard, B. E. (1980) Neuropharmacology 19: 1175–1183

Montgomery, S. A. (1980) Ibid. 19: 1185–1190

Ross, S. B., Ögren, S. O., Renyi, A. L. (1976) Acta Pharmacol. Toxicol. Kbh 34: 152–166

Tang, S. W., Seeman, P. (1980) Naunyn-Schmiedeberg's Arch. Pharmacol. 311: 255–261

Turski, L., Czuczwar, S. J., Turski, W., Kleinrok, Z. (1981a) Psychopharmacology 73: 81–83

Turski, L., Turski, W., Czuczwar, S. J., Kleinrok, Z. (1981b) Ibid. 73: 376–380

Turski, L., Czuczwar, S. J., Turski, W., Kleinrok, Z. (1981c) Neuropharmacology in the press