J. Pharm. Pharmac., 1969, **21**, 845–847 *Received June* 9, 1969

On the role of a central adrenergic mechanism in morphine analgesic action

YU. P. VEDERNIKOV AND I. I. AFRIKANOV

The Department of Pharmacology, Medical Institute, Sverdlovsk, U.S.S.R.

The influence of drugs interfering with brain monoamine metabolism on morphine analgesia of rats was estimated by the tail pressure method. Central adrenergic stimulation produced by apomorphine, cocaine, pyrogallol or amphetamine led to stereotyped behaviour and elevation of the pain threshold. Lower doses of these drugs potentiated morphine analgesic action. Reserpine, iproniazid and disulfiram weakened morphine analgesic action. α-Methyldopa increased morphine action and (±)-tryptophan did not influence it significantly.

Reserpine depletes brain catecholamine stores and antagonizes morphine analgesia (Schneider, 1954; Radouco-Thomas, Radouco-Thomas & LeBreton, 1957; Schaumann, 1958; Paeile & Munoz, 1966; Verri, Graeff & Corrado, 1967; Raevsky, 1969), so, too, does tetrabenazine (Takagi, Takashima & Kimura, 1964). On the other hand, Rudzik & Mennear (1965) believe that the antagonism of morphine by reserpine is not due to its action on catecholamine metabolism. A possible role of 5-hydroxytryptamine (5-HT) in morphine analgesia has also been considered (Medacović & Banić, 1964; Nićak, 1965). We now describe the relation between drugs which interfere with brain noradrenaline metabolism and morphine analgesic action.

EXPERIMENTAL

Analgesic activity of morphine was estimated by the change in pain threshold when mechanical pressure was applied to the tails of groups of ten white female rats, 150–220 g (Sangailo, 1962). The drugs, their doses, time and route of administration, are given in Table 1.

RESULTS AND DISCUSSION

The results are in Table 1 and illustrated in Figs. 1 and 2. We also found that apomorphine, 3–5 mg/kg, produced stereotypy and elevation in pain threshold and that amphetamine, 2 mg/kg, activated rats without producing any action on pain threshold, although at higher doses it produced stereotypy and raised the pain threshold. Also, α-methyldopa depressed the rats and elevated the pain threshold. Where the pain threshold increased, morphine was injected after the threshold had returned to the initial level.

Since Vogt's (1954) discovery of the depleting action of morphine on brain catecholamine, and Schneider's (1954) study of reserpine antagonism of morphine analgesia, the question of the significance of brain catecholamines in morphine action has attracted much attention (Radouco-Thomas & others, 1957; Schaumann, 1958; Takagi & others, 1964; Paeile & Munoz, 1966; Verri & others, 1967; Takagi & Nakama, 1966, 1968; Raevsky, 1969; Zakusov, 1969).

Table 1. *Doses, route and time of drug administration before morphine and its influence on morphine effect*

Drugs	Dose (mg/kg)	Route	Time before morphine (h)	Morphine HCl (mg/kg, s.c.)	Influence on morphine effect: Increase	Influence on morphine effect: Decrease
Pyrogallol	50	s.c.	1	2·5	+*	
Cocaine HCl	50	s.c.	1	2·5	+*	
(±)-Tryptophan	400	i.p.	4	2·5	+	
(±)-Tryptophan	400	i.p.	4	5·0	+	
α-Methyldopa	400	i.p.	23	2·5	+*	
α-Methyldopa	100	i.p.	4	4·0	+*	
Amphetamine	2	s.c.	1	2·5	+*	
Amphetamine	2	s.c.	1	4·0	+*	
Disulfiram	50	i.p.	2	2·5		−
Disulfiram	50	i.p.	2	4·0		−*
Iproniazid	100	i.p.	4	2·5		−*
Iproniazid	100	i.p.	8	5·0		−*
Reserpine	1	i.p.	8	5·0		−*

* Significant ($P < 0·05$).

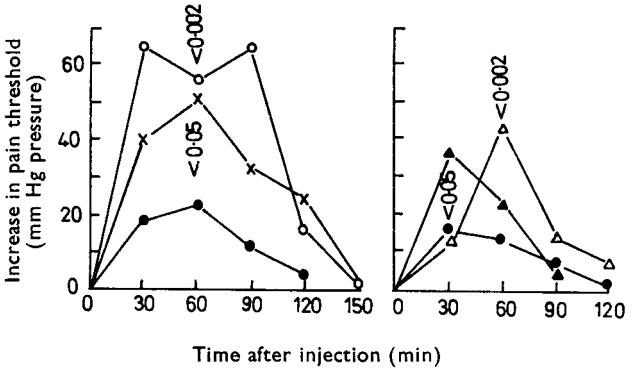

FIG. 1. Interaction of some drugs, interfering with brain noradrenaline metabolism and morphine. Each point represents the means of ten animals treated with morphine, 2·5 mg/kg alone (●) and morphine after pyrogallol (○), cocaine (×), α-methyldopa, 400 mg/kg (▲), amphetamine (△). Doses and routine are in Table 1.

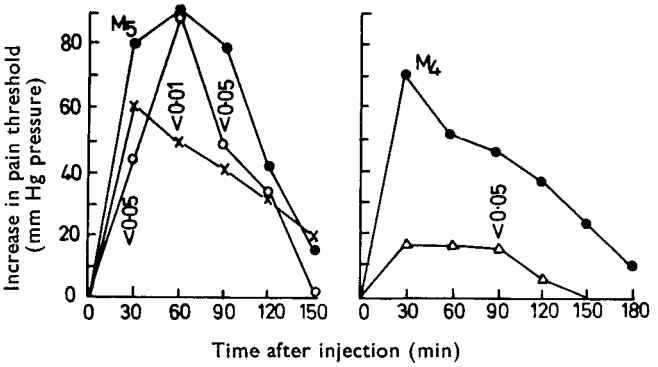

FIG. 2. Interaction of some drugs, interfering with brain noradrenaline metabolism and morphine. Morphine, 4 mg/kg (M_4) and 5 mg/kg (M_5) action on pain threshold and change in activity after reserpine (○), iproniazid (×) and disulfiram (△). Doses and routine are in Table 1.

Inhibition of the re-uptake process by cocaine or depression of catechol-*O*-methyl transferase by pyrogallol (Fig. 1) or by apomorphine (Belenkii & others, 1966) produced stereotypy and elevated the pain threshold. In doses having no visible effect on behaviour (Table 1), these drugs potentiated the analgesic effect of morphine. It seems likely that the described effects follow the increase of noradrenaline at the receptor sites. It seems significant that iproniazid antagonized morphine analgesia, since inhibition of monoamine oxidase could inhibit release, reduce the rate of turnover or deplete the brain noradrenaline stores (see Glowinski & Baldessarini, 1966). The ability of amphetamine to potentiate morphine analgesia and evoke stereotype behaviour and elevation in the pain threshold after increasing the dose results from its direct and indirect sympathomimetic activity. Reserpine, by depleting noradrenaline from the brain, weakened morphine analgesic action significantly 30 and 90 min after morphine administration, while the maximum activity remained unchanged (Fig. 2).

Disulfiram, an inhibitor of dopamine-β-hydroxylase, inhibited morphine analgesia probably by depressing the noradrenaline formation from dopamine. α-Methyldopa increased the pain threshold. Morphine after the threshold returned to the initial level, caused a greater elevation of pain threshold than it did alone.

Tryptophan, a precursor of 5-HT, increased morphine analgesic action but not significantly.

From the results it may be concluded that central sympathetic activation can elevate the pain threshold. Drugs which increased noradrenaline concentration at the receptor sites potentiated, and the drugs which decreased it weakened, morphine analgesic action.

On the basis of the results obtained we support the idea that morphine analgesia is a result of liberation of noradrenaline from the brain stores. The direct action of morphine on the central adrenostructures may be kept in mind, but this mechanism seems to be less important.

REFERENCES

Belenkii, M, L., Vitolina, M. R., Baumanis, E. (1966). *Bull. exp. Biol. Med. U.S.S.R.*, **61**, 54–55.

Contreras, M. E., Quiyada, L. & Tamayo, L. (1967). *Medna. Pharmac. Exp.*, **16**, 371–376.

Glowinski, J. & Baldessarini, R. (1966). *Pharmac. Rev.*, **18**, 1201–1238.

Haefely, W., Hürlinmann, A. & Thoenen, H. (1967). *Br. J. Pharmac. Chemother.*, **31**, 105–119.

Holtz, P. & Palm, D. (1967). *Life Sci.*, **6**, 1847–1857.

Medacović, M. & Banić, B. (1964). *J. Pharm. Pharmac.*, **16**, 198–206.

Nićak, A. (1965). *Medna Pharmac. Exp.*, **13**, 43–48.

Paeile, C. & Munoz, C. (1966). *III Intern. Pharmac. Congr., Abstr.*, 66.

Radouco-Thomas, S., Radouco-Thomas, C. & LeBreton, E. (1957). *Arch. exp. Path. Pharmak.*, **232**, 279–291.

Raevsky, K. (1969). *Farmak. Toxs.*, **32**, 134–137.

Rudzik, A. & Mennear, J. (1965). *J. Pharm. Pharmac.*, **17**, 326–327.

Sangailo, A. K. (1962). *Proc. of Sverdlovsk Medical Inst.*, 35, 5.

Schaumann, W. (1958). *Arch. exp. Path. Pharmak.*, **235**, 1–9.

Schneider, J. A. (1954). *Proc. Soc. exp. Biol.*, **87**, 614–615.

Takagi, H., Takashima, T. & Kimura, K. (1964). *Archs int. Pharmacodyn. Thér.*, **149**, 484–492.

Takagi, H. & Nakama, M. (1966). *Jap. J. Pharmac.*, **16**, 483–484.

Takagi, H. & Nakama, M. (1968). *Ibid.*, **18**, 54–58.

Verri, R. A., Graeff, G. & Corrado, A. P. (1967). *J. Pharm. Pharmac.*, **19**, 264–265.

Vogt, M. (1954). *J. Physiol. Lond.*, **123**, 451–481.

Zakusov, V. V. (1969). *Farmak. Toxs.*, **32**, 131–134.