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Tryptamine-induced drug effects insensitive to serotoninergic antagonists: evidence of specific tryptaminergic receptor stimulation?

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The drug effects of tryptamine and 5-hydroxytryptophan (5-HTP) in the rabbit were compared following monoamine oxidase inhibition and various drug pretreatments. Both agents evoked hyperthermia and behavioural excitation; tryptamine but not 5-HTP also produced forepaw clonic activity. Serotoninergic receptor blockers abolished the effects of 5-HTP but only weakly influenced tryptamine responses. Both tryptamine and 5-HTP effects were potentiated by fluoxetine. Methergoline, a putative tryptaminergic receptor blocker, antagonized tryptamine-induced hyperthermia and forepaw clonus but did not influence 5-HTP responses. It is postulated that while 5-HTP produces its effects through a serotoninergic mechanism, some of the responses to tryptamine result from activation of a specific tryptamine-sensitive mechanism.

The thermotropic effects of 5-hydroxytryptamine (5-HT) and 5-hydroxytryptophan (5-HTP) in the rabbit have long been used as an index of central serotoninergic activity. Horita & Gogerty (1958) used the rabbit to compare the hyperthermic effects of 5-HTP and lysergic acid diethylamide (LSD), and concluded that the two shared a common mechanism of action. Jacob & associates (1971, 1972, 1973) also used the rabbit to elucidate central serotoninergic mechanisms and to define the interrelations of 5-HT with catecholaminergic and cholinergic systems. 5-HTP-induced hyperthermia has also been used to test the efficacy of possible peripherally-acting inhibitors of decarboxylase enzyme (Horita & Hamilton, 1970; Gardey-Levassort & Lechat, 1974; Gardey-Levassort, Olive & Lechat, 1974).

Whether tryptamine stimulates 5-HT receptors or its own receptor entity is a matter of speculation (Gaddum, 1953; Woolley & Shaw, 1957; Winter & Gessner, 1968; Pourrias, 1975; Dooley & Quock, 1976). In the central nervous system (cns), its unique regional distribution and its selective alteration by drug intervention suggest that it is not restricted to storage in serotoninergic neurons (Knott, Marsden & Curzon, 1974), and that it may possess functions of its own rather than being a metabolite of 5-HT (Saavedra & Axelrod, 1974).

We have compared the effects of tryptamine and 5-HTP in the rabbit hyperthermia model and examined whether the thermotropic effects of tryptamine might be explained by an interaction with serotoninergic receptors.

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MATERIALS AND METHODS

Male New Zealand rabbits, 1·8–2·5 kg, were restrained in open wooden stanchions (Shellenberger & Elder, 1967), while colonic temperatures were electronically monitored with flexible rectal thermistor probes inserted to 12 cm and taped to the tail. Animals were conditioned to stanchion restraint for 6–8 h on the day before the experiment. Room temperature was 23·0° ± 1·0°.

The drugs used were gifts of: Merrell-National (pheniprazine hydrochloride), Eli Lilly (fluoxetine hydrochloride), Squibb (cinanserin hydrochloride), Merck Sharp and Dohme (cyproheptadine hydrochloride), Sandoz (D-2-bromolysergic acid diethylamide, BOL) and Farmitalia (methergoline). Tryptamine hydrochloride and 5-hydroxytryptophan were purchased from Regis Chemical Company. With the exception of BOL, which was supplied in injection ampoules, all drugs were prepared in aqueous solution. Methergoline was solubilized in distilled water made acidic with a slight excess of ascorbic acid (Ferrini & Glasser, 1965). Drugs were administered intravenously at 1·0 ml kg^{-1}.

RESULTS

Tryptamine- and 5-HTP-induced drug effects

Rabbits administered increasing doses of tryptamine responded with transient episodes of behavioural excitation, polypnea and mydriasis, 5·0 mg kg^{-1}

produced virtually no change in colonic temperature, while 10·0 mg kg^{-1} elevated temperature approximately 0·5° (Fig. 1). While these responses

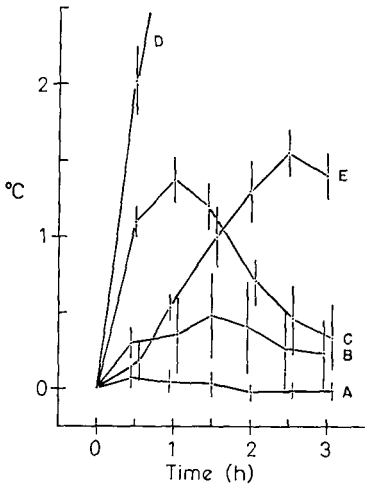

FIG. 1. Influence of tryptamine and 5-HTP on rabbit body temperature. Each point represents the mean colonic temperature (°C) of at least 6 rabbits following treatment with: A, tryptamine (5·0 mg kg^{-1}); B, tryptamine (10·0 mg kg^{-1}); C, pheniprazine (5·0 mg kg^{-1}) + tryptamine (2·5 mg kg^{-1}); D, pheniprazine + tryptamine (5·0 mg kg^{-1}); and E, pheniprazine + 5-HTP (5·0 mg kg^{-1}). Vertical lines represent the s.e.m.

were fleeting and unimpressive, pretreatment (120 min) with pheniprazine (5·0 mg kg^{-1}) intensified the effects; 1 h after 2·5 mg kg^{-1} of tryptamine, temperature was elevated to a maximum of 1·4°. Concommitantly, the rabbits exhibited prolonged behavioural stimulation, mydriasis and blepharodiastasis, tachypnoea, constriction of the ear vasculature and prominent oscillations or 'piano-playing' movements of the extended forelimbs. Administration of 5·0 mg kg^{-1} of tryptamine to pheniprazine-pretreated rabbits evoked a lethal hyperpyrexic reaction accompanied by grossly-exaggerated behavioural, autonomic and forepaw clonic activities. But 5·0 mg kg^{-1} of 5-HTP given to pheniprazine-pretreated rabbits produced mild behavioural stimulation, mydriasis, respiratory stimulation and or vasodilatation of the ears. Neither 5·0 nor 10·0 mg kg^{-1} produced 'piano-playing' forepaw activity.

Influence of serotoninergic antagonists upon tryptamine- and 5-HTP-induced drug effects

Pheniprazine-pretreated rabbits were additionally administered cinanserin (5·0 mg kg^{-1}, 30 min), cyproheptadine (2·0 mg kg^{-1}, 30 min) or BOL (1·0 mg kg^{-1}, 60 min) after pheniprazine. Cinanserin and cyproheptadine both reduced colonic temperature by approximately 0·5° for 60 min. When these animals were administered a standard challenge dose of 2·5 mg kg^{-1} of tryptamine, they responded with a slightly-diminished hyperthermia (Fig. 2),

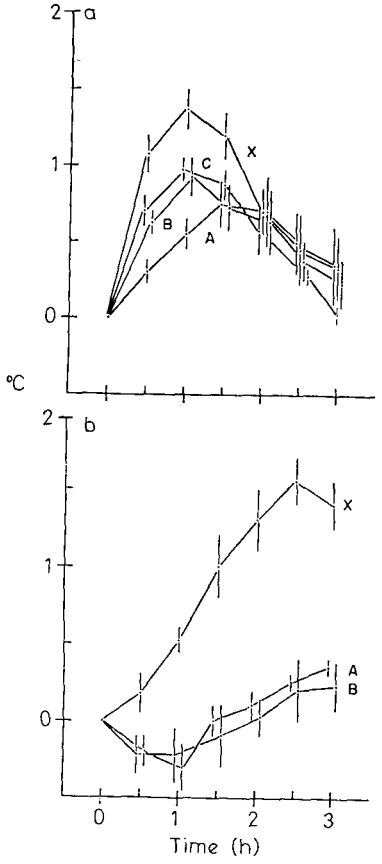

FIG. 2. Influence of serotoninergic antagonists upon a: tryptamine-and b: 5-HTP-induced hyperthermia. Each point represents the mean colonic temperature (°C) of at least 6 rabbits following treatment with: X, pheniprazine + tryptamine or 5-HTP; A, cinanserin + pheniprazine + tryptamine or 5-HTP; B, cyproheptadine + pheniprazine + tryptamine or 5-HTP; and C, BOL + pheniprazine + tryptamine. Refer to text for doses and times of antagonists. Vertical lines represent the s.e.m.

though the behavioural, autonomic and forepaw clonic effects remained intact. By comparison identical doses of cinanserin and cyproheptadine, abolished the hyperthermic and behavioural reactions to a challenge dose of 5·0 mg kg^{-1} of 5-HTP.

Influence of a 5-HT-uptake inhibitor upon tryptamine- and 5-HTP-induced drug effects

Rabbits pretreated with pheniprazine + fluoxetine (5·0 mg kg^{-1}, 120 min) showed a marked potentiation of the hyperthermic and behavioural effects seen with both tryptamine and 5-HTP and ultimately succumbed to fatal hyperpyrexia (Fig. 3).

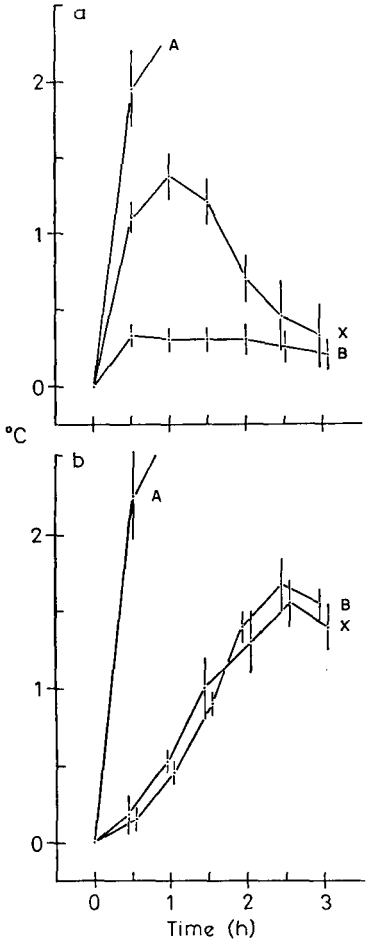

FIG. 3. Influence of fluoxetine and methergoline upon a: tryptamine- and b: 5-HTP-induced hyperthermia. Each point represents the mean colonic temperature (°C) of at least 6 rabbits following treatment with: X, pheniprazine + tryptamine or 5-HTP; A, fluoxetine + pheniprazine + tryptamine or 5-HTP; and B, methergoline + pheniprazine + tryptamine or 5-HTP. Refer to text for doses and times of antagonists. Vertical lines represent the s.e.m.

Influence of a tryptaminergic antagonist upon tryptamine- and 5-HTP-induced drug effects

Rabbits were concommitantly pretreated with pheniprazine and methergoline (1·0 mg kg^{-1}, 120 min). After 2·5 mg kg^{-1} of tryptamine, there was a significantly attenuated hyperthermic effect (Fig. 3) with continued exhibition of behavioural excitation, but no 'piano-playing' forepaw movements. Methergoline pretreatment had no influence upon the temperature or the behavioural responses to 5-HTP.

DISCUSSION

The stimulatory influence of tryptamine upon behaviour and autonomic function has long been recognized (Laidlow, 1912). There is evidence in favour of a common peripheral receptor for tryptamine and 5-HT (Gaddum, 1953; Woolley & Shaw, 1953). More recent investigations by Pourrias (1975) and Dooley & Quock (1976) show that tryptamine-induced hypertension and hypothermia, respectively, result from tryptamine activation of peripheral serotoninergic receptors. Separate peripheral receptors for these indoleamines have also been suggested (Woolley & Shaw, 1957; Winter & Gessner, 1968; Frankhuijzen & Bonta, 1974).

In the chronic spinal dog, Martin & associates (1970, 1972, 1975, 1976) have identified a specific tryptamine pathway in the spinal cord, differentiated between tryptamine and 5-HT involvement in the flexor reflex response, and postulated that LSD-like psychotogens in this preparation act via the tryptamine, not the 5-HT, mechanism. Vogel & Chen (1977) also established a correlation between tryptamine and certain psychotogens in their rat model.

The present work pharmacologically differentiates tryptamine from 5-HT responses and reaffirms that 5-HTP-induced hyperthermic and behavioural effects in the rabbit are primarily serotoninergic. Cinanserin cyproheptadine pretreatment was effective in attenuating the hyperthermia, an observation consistent with the findings of Rubin, Piala & others (1964) and Jacob & associates (1971, 1973). In demonstrating the similarities and cross-tolerance phenomenon between 5-HTP and LSD in the rabbit, Horita & Gogerty (1958) also showed BOL to be active in antagonizing 5-HTP-induced hyperthermia. However, these same pretreatments with cinanserin, cyproheptadine and BOL in effective anti-5-HTP doses were only weakly antagonistic towards tryptamine-induced hyperthermia. Moreover, tryptamine-induced behavioural excitation and 'piano-playing' effects were not appreciably affected. The failure of these antagonists to reduce these drug effects prompted consideration of the possibility that these responses were not generated by an action of tryptamine upon serotoninergic receptors.

Tryptamine-induced forepaw clonic activity was

described by Tedeschi, Tedeschi & Fellows (1959). It is relatively insensitive to inhibition by serotoninergic receptor blockers. But one active antagonist, methergoline was synthesized as a serotoninergic receptor blocker (Beretta, Glasser & others, 1965; Ferrini & Glasser, 1965). Clineschmidt & Lotti (1974) found that methergoline was active against tryptamine-induced forepaw clonus at doses which did not affect 5-HTP-induced head twitching; the same investigators found cinanserin and cyproheptadine to be more active against the 5-HT function than the tryptamine response. They concluded that in certain test systems, methergoline has greater specificity for blocking tryptamine receptors than 5-HT receptors. In the present study, pretreatment of rabbits with methergoline resulted in significant antagonism of tryptamine-induced forepaw clonus as well as hyperthermia; identical pretreatment, however, failed to influence 5-HTP-induced drug effects. This lack of antagonistic effect against 5-HTP-induced hyperthermia was also reported by Beretta, Ferrini & Glasser (1965). Since methergoline inhibited tryptamine but not 5-HTP and since, conversely, serotoninergic antagonists blocked 5-HTP and had less influence upon tryptamine, it would appear that the tryptamine-induced forepaw clonic and hyperthermic responses in the rabbit result from tryptamine, not serotoninergic, receptor stimulation.

In addition, fluoxetine, a selective inhibitor of the 5-HT neuronal uptake process (Wong, Horng & others, 1974), was found to markedly potentiate the effects of tryptamine and 5-HTP. Since reuptake is the primary means of terminating the actions of monoamines in the cns, this observation can be interpreted to mean that tryptamine is inactivated by uptake into serotoninergic neurons, or that fluoxetine is, more accurately-speaking, an inhibitor of an 'indoleaminergic' rather than a specific serotoninergic uptake mechanism.

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REFERENCES

BERETTA, C., FERRINI, R. & GLASSER, A. H. (1965). *Nature*, **207**, 421–422.
BERETTA, C., GLASSER, A. H., NOBILI, M. B. & SILVESTRINI, E. (1965). *J. Pharm. Pharmac.*, **17**, 423–428.
CLINESCHMIDT, B. V. & LOTTI, V. J. (1974). *Br. J. Pharmac.*, **50**, 311–313.
DOOLEY, D. J. & QUOCK, R. M. (1976). *J. Pharm. Pharmac.*, **28**, 775–776.
FRANKHUIJZEN, A. L. & BONTA, I. L. (1974). *Eur. J. Pharmac.*, **26**, 210–230.
FERRINI, R. & GLASSER, A. (1965). *Psychophatmac.*, **8**, 271–276.
GADDUM, J. H. (1953). *J. Physiol.*, **119**, 363–368.
GARDEY-LEVASSORT, C. & LECHAT, P. (1974). *J. Pharm. Pharmac.*, **26**, 278–279.
GARDEY-LEVASSORT, C., OLIVE, G. & LECHAT, P. (1974). *Pharmacology*, **11**, 268–277.
HORITA, A. & GOGERTY, J. H. (1958). *J. Pharmac. exp. Ther.*, **122**, 195–200.
HORITA, A. & HAMILTON, A. E. (1970). *J. Pharm. Pharmac.*, **22**, 389–391.
JACOB, J., GIRAULT, J. M. & CLARET, B. (1971). *J. Pharmac.*, **2**, 232–233.
JACOB, J., GIRAULT, J. M. & PEINDARIES, R. (1972). *Neuropharmac.*, **11**, 1–16.
JACOB, J. & PEINDARIES, R. (1973). In: *The Pharmacology of Thermoregulation*, p. 202. Editors: Schönabum, E. & Lomax, P. Basel: Karger.
KNOTT, P. J., MARSDEN, C. A. & CURZON, G. (1974). *Adv. Biochem. Psychopharmac.*, **11**, 109–114.
LAIDLOW, P. P. (1912). *Biochem. J.*, **6**, 141–150.
MARTIN, W. R. & EADES, C. G. (1970). *Psychopharmac.*, **17**, 242–257.
MARTIN, W. R. & EADES, C. G. (1972). *Ibid.*, **27**, 93–98.
MARTIN, W. R., SLOAN, J. W., BUCHWALD, W. F. & CLEMENTS, T. H. (1975). *Ibid.*, **43**, 131–134.
MARTIN, W. R., THOMPSON, J. A. & NOZAKI, M. (1976). *Life Sci.*, **19**, 1383–1386.
POURRIAS, B. (1975). *J. Pharmac.*, **6**, 153–164.
RUBIN, B., PIALA, J. J., BURKE, J. C. & CRAVER, B. N. (1964). *Archs int. Pharmacodyn. Ther.*, **152**, 131–142.
SAAVEDRA, J. M. & AXELROD, J. (1974). *Adv. Biochem. Psychopharmac.*, **10**, 135–139.
SHELLENBERGER, M. K. & ELDER, J. T. (1967). *J. Pharmac. exp. Ther.*, **158**, 219–226.
TEDESCHI, D. H., TEDESCHI, R. E. & FELLOWS, E. J. (1959). *Ibid.*, **126**, 223–232.
VOGEL, W. H. & COHEN, I. (1977). *Brain Res.*, **122**, 162–164.
WINTER, J. C. & GESSNER, P. K. (1968). *J. Pharmac. exp. Ther.*, **162**, 286–293.
WONG, D. T., HORNG, J. S., BYMASTER, F. P., HAUSER, K. L. & MOLLOY, B. B. (1974). *Life Sci.*, **15**, 471–479.
WOOLLEY, D. W. & SHAW, E. (1953). *J. biol. Chem.*, **203**, 69–79.
WOOLLEY, D. W. & SHAW, E. (1957). *J. Pharmac. exp. Ther.*, **121**, 13–17.