Quipazine: a serotoninergic hyperthermic agent in the rabbit

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Quipazine (2-(1-piperazinyl)-quinoline) was first described as a non-ergot oxytocic agent that might interact with serotoninergic (5-HT) mechanisms (Hong & Pardo, 1966). Subsequent research demonstrated that quipazine did indeed stimulate serotoninergic receptors in both peripheral tissues (Hong, Sancillo & Vargas, 1969) and the central nervous system (Rodriguez, 1972; Rodriguez, Rojas-Ramirez & Drucker-Colin, 1973). More recently, it has been reported that quipazine blocks the uptake of 5-HT and dopamine into rat striatal tissue *in vitro* and, hence, might possess some anti-Parkinsonian potential (Medon, Leeling & Phillips, 1973). It has also been suggested that quipazine might also interact with central dopaminergic systems since it induces behavioural symptoms in rats similar to those caused by dopaminergic agents; furthermore, these quipazine-induced responses were blocked by selective dopaminergic antagonists (Grabowska, Antkiewicz & Michaluk, 1974).

Rabbit body temperature has been shown to increase in response to treatment with (+)-amphetamine (Hill & Horita, 1971), apomorphine (Hill & Horita, 1972) and other dopaminergic agonists (Quock, unpublished observations). Whether quipazine produces a hyperthermic response in rabbits and whether this hyperthermia might be sensitive to antagonism by centrally-acting receptor blocking agents have now been examined.

Male New Zealand rabbits, 2·0–2·5 kg, were restrained in open wooden stanchions (Shellenberger & Elder, 1967) while body temperature was electronically monitored and automatically recorded. Room temperature was constant at 22·0° ± 1·0°. Quipazine (Miles Laboratories), cyproheptadine (Merck Sharp & Dohme) and 3-(*p*-trifluoromethylphenoxy)-*N*-methyl-3-phenylpropylamine hydrochloride (Lilly 110140) (Lilly) were prepared in aqueous solution immediately before injection. Haloperidol (McNeil Laboratories) and 2-bromolysergic acid diethylamide (BOL-148) (Sandoz Pharmaceuticals) were acquired in pre-prepared ampoules and diluted to appropriate concentrations with distilled water. All drug solutions were administered intravenously in a volume of 1·0 ml kg^{-1}.

In one experiment, intravenous administration of increasing doses of quipazine resulted in hyperthermic responses of increasing magnitudes (Fig. 1A). Lethality was 50% at 5·0 mg kg^{-1} and 100% at 10·0 mg kg^{-1}. After treatment with a standard dose of 2·5 mg kg^{-1}, body temperature rose, reaching a peak at 2 h, and returned to base line after a further 5 h. Mydriasis was immediately evident after injection of the drug and lasted 1–2 h. An increased rate of respiration and constriction of the ear vasculature appeared within 15 min of injection and lasted about 3–4 h. Behaviourally, the animal became alert, assumed a standing rather than crouching posture and was instantly responsive to visual or auditory cues. There was no spontaneous body movement in these animals but the rabbits' heads would immediately turn towards the direction of any sudden movement or sound. Rabbits injected with lethal doses of quipazine exhibited similar behavioural and autonomic signs, eventually assuming a prostrate position with deep and rapid respiration. Behavioural excitation was not observed at any dose of quipazine.

In another experiment, rabbits were pretreated with haloperidol (0·5 mg kg^{-1}), cyproheptadine (2·0 mg kg^{-1}), BOL-148 (1·0 mg kg^{-1}) or Lilly 110140 (5·0 mg kg^{-1}).

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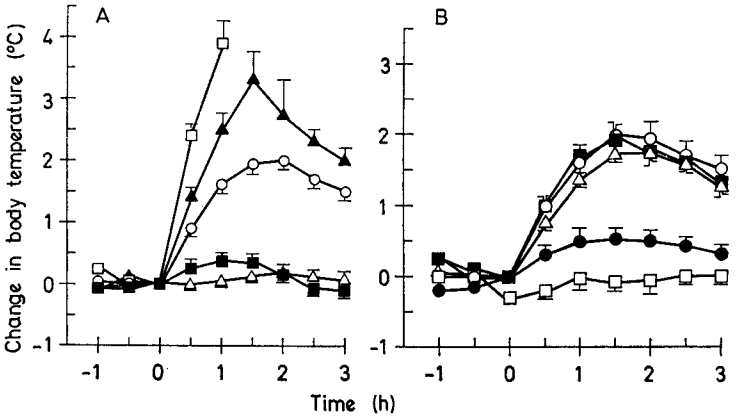

FIG. 1 The influence of quipazine on body temperature in (A) naive rabbits injected with quipazine solutions intravenously at zero time; (B) rabbits pretreated with various blocking agents. Each point represents the mean body temperature of at least 6 rabbits after: (A) the injection of distilled water (△), quipazine, 0.5–1.0 (■), 2.5 (○), 5.0 (▲), or 10.0 mg kg^{-1} (□); (B) pretreatment with distilled water (○), haloperidol (■), cyproheptadine (□), BOL–148 (●), or Lilly 110140 (△). Refer to text for doses. The vertical lines indicate s.e.m.

Of these four drugs, only cyproheptadine exerted thermotropic activity when administered alone; it lowered body temperature 0·5° over 60 min and mildly sedated the animals. The dopaminergic receptor blocker haloperidol in doses sufficient for antagonism of apomorphine-induced hyperthermia in rabbits (Roszell & Horita, 1975) failed to influence quipazine-induced hyperthermia. The serotoninergic antagonists cyproheptadine and BOL-148 in doses sufficient to block LSD-induced hyperthermia in rabbits (Horita & Gogerty, 1958) prevented the temperature response to quipazine, although the behavioural and autonomic effects of the drug appeared to remain unaltered. The selective 5-HT uptake blocker Lilly 110140, in doses sufficient to abolish fenfluramine-induced hyperthermia (Quock, in preparation), was ineffective in altering quipazine-induced (2·5 mg kg^{-1}) temperature changes (Fig. 1B).

These data suggest that quipazine-induced temperature effects result from activation of serotoninergic and not dopaminergic mechanisms in the rabbit. The failure of Lilly 110140 to influence the hyperthermia indicates that quipazine acts directly upon serotoninergic receptors rather than through the release of transmitter from 5-HT-containing nerve terminals. These findings are consistent with earlier reports of central serotoninergic receptor stimulation by quipazine (Rodriguez & others, 1973). We are also in agreement with a recent opinion that certain pharmacological actions of quipazine may represent not only central dopaminergic activity but also central serotoninergic processes (Costall & Naylor, 1975).

Another central serotoninergic agonist in the rabbit seems to be LSD (Horita & Gogerty, 1958). LSD produces a marked hyperthermic response as well as extreme behavioural excitation, characterized by an increased level of spontaneous locomotor activity; both these effects are antagonized by pretreatment with serotoninergic receptor blockers (Horita & Gogerty, 1958). The reason why quipazine should share the hyperthermic action but not the behavioural excitatory effect of LSD is presently unknown. It is possible that the serotoninergic receptors which mediate temperature and behavioural effects in the rabbit are not the same and that quipazine acts selectively upon the temperature-modifying serotoninergic receptor. Further research involving central microinjection work in rabbits is currently in progress in an effort to better understand serotoninergic mechanisms within the central nervous system.

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Sex specific differences in noradrenaline uptake and its inhibition by maprotiline

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Presynaptic uptake inhibition of monoamines by tricyclic drugs (with the exception of iprindole) is considered to be the main characteristic of their mode of action relevant to antidepressant activity. The extent of uptake inhibition of noradrenaline and/or 5-hydroxytryptamine (5-HT) varies with each drug and its metabolites. Maprotiline (Ludiomil, CIBA-Geigy) is a new tetracyclic antidepressant (Kielholz, 1972) which inhibits only noradrenaline uptake, not affecting 5-HT uptake even at high concentrations (Maître, Waldmeier & others, 1974). It thus provides a tool for investigating the role of selective noradrenaline uptake inhibition in biochemical subgroups of endogenous depression (Pühringer, Wirz-Justice & Hole, 1975).

Although extensively studied pharmacologically, *in vitro* monoamine uptake has not been systematically studied to elucidate naturally occurring changes: circadian (Wirz-Justice, 1974; Endersby & Wilson, 1974) and possible seasonal (Wirz-Justice, 1974) variations have been observed, but the influence of sex and endocrinological state is not known. This may be an important factor, particularly since application of steroid hormones has been found to influence uptake (Endersby & Wilson, 1974; Wirz-Justice, Hackmann & Lichtsteiner, 1974). Therefore it seemed useful to investigate *in vitro* noradrenaline uptake to determine the extent, if any, of sex-specific differences in uptake and its inhibition by maprotiline.

Male (350 g) and female (250 g) rats were kept at least one month in a controlled environment (lights on from 05.00 to 19.00 h; temp. 24 $\pm$ 1·5°), and had free access to food. Only females having at least two consecutive regular four-day oestrus cycles (controlled by daily vaginal smears before 08.30 h) were used on the morning of pro-oestrus. Both male and female rats were killed at 10 h, and the brain regions