Decrease of food intake by quipazine in the rat: relation to serotoninergic receptor stimulation

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On the basis of pharmacological and biochemical data (Hong, Sancilio & others, 1969; Rodríguez, Rojas-Ramírez & Drucker-Colín, 1973; Grabowska, Antkiewicz & Michaluk, 1974) it has been suggested that quipazine, a new type of antidepressant drug (Rodríguez & Pardo, 1971), can directly stimulate 5-hydroxytryptamine (5-HT) receptors in the brain.

Since 5-HT appears to be involved in the regulation of food intake in various animal species (see review by Baile, 1974) as well as in the anorectic activity of fenfluramine (Samanin, Ghezzi & others, 1972; Jespersen & Scheel-Krüger, 1973; Kruk, 1973; Cline-schmidt, 1973; Garattini, Bizzi & others, 1975a; Garattini, Buczko & others, 1975b), it was speculated that quipazine might affect the food intake of rats as a consequence of its ability to mimic 5-HT activity.

The present experiments were undertaken in an attempt to verify this hypothesis.

Female Charles River rats, 200–250 g, were caged singly and trained for 9 days to take their daily food during 6 out of 24 h (water *ad lib*). On the day of the experiment, the animals were injected intraperitoneally with methergoline 3 mg kg^{-1}, or with an equal volume of the vehicle (carboxymethylcellulose 0·5 %). Three h later they received intraperitoneally various doses of quipazine (2·5, 5 and 10 mg kg^{-1}) or saline and were immediately placed in a cage containing a weighed amount of food. Two h later the animals were removed and the food weighed again to the nearest 0·1 g. The difference between the food left and the original amount constituted the measure of the food intake.

A group of animals was lesioned in the nucleus raphé medianus (MR) by using a 2·5 mA direct current for 15 s with a stainless steel electrode (tip 0·5 mm; diameter 0·2 mm) implanted stereotaxically according to the following coordinates: A 0·4; L 0; H-2·6 (König & Klippel, 1963). Controls were similarly operated upon but not lesioned. After a recovery period of 3 days, these animals were trained as described above and on the day of the experiment they were injected intraperitoneally with 10 mg kg^{-1} of quipazine or saline for food intake testing.

24 h from the end of the experiments, all the animals were killed and their brains quickly removed and divided in two parts at the midbrain level. The forebrain was used for the fluorimetric determination of 5-HT according to Giacalone & Valzelli (1969). The remaining brainstem (midbrain + pons + medulla oblongata) of MR lesioned rats was used for the histological examination of the lesion location. The food intake data were analysed statistically by a two way (2 × 4) between-subjects analysis of variance followed by Tukey's test.

Quipazine was kindly supplied by Miles Lab. Inc., U.S.A. and methergoline by Farmitalia (Italy).

In agreement with the observation of Hong & Pardo, (1966), quipazine produced no overt behavioural change in the animals, with the exception of a moderate increase of exploratory activity which was observed for a few minutes at the higher dose used (10 mg kg^{-1}).

As shown in Table 1, quipazine produced a dose-dependent reduction of food intake in rats. This effect was significantly antagonized by a pretreatment with methergoline.

In Table 2 the data obtained with the animals lesioned in the MR are reported. The effect of quipazine (10 mg kg^{-1}, i.p.) was not significantly affected by the MR lesion. The histological examination showed that the lesions were generally confined to the desired area; however, a few animals in which the lesion was not properly located were excluded for the experiments. The forebrain concentration of 5-HT in sham operated and MR lesioned animals were respectively: 0·32 ± 0·01 and 0·11 ± 0·02 ($\mu g\ g^{-1}$ ± s.e.).

Quipazine is a powerful agent in reducing food intake in rats at doses between 2·5 and 10 mg kg^{-1} (i.p.). This effect is inhibited by a previous administration of methergoline, a drug showing central anti-5-HT activities (Mawson & Whittington, 1970) but not by an electrolytic lesion of the nucleus raphé medianus, which is known to be an important site of origin of

Table 1. *The effect of methergoline on the decrease of food intake induced by quipazine in the rat.*

Treatment	mg kg^{-1}, i.p.	Food intake (g per rat ± s.e.) Control	Experimental[a]
Saline	—	8·3 ± 0·4	7·5 ± 0·8
Quipazine	2·5	5·9 ± 0·7	7·3 ± 0·4
Quipazine	5·0	3·3 ± 0·4†	7·6 ± 0·7*
Quipazine	10·0	2·0 ± 0·5†	6·3 ± 0·4*

Each value represents the mean of 2 h food intake of 6 animals.

([a]) = The animals received methergoline (3 mg kg^{-1}, i.p.) or an equal volume of the vehicle 3 h before quipazine.

* $P < 0·001$ when compared with control.

† $P < 0·01$ when compared with saline.

* Correspondence.

Table 2. *The effect of quipazine on food intake of rats lesioned in the nucleus raphé medianus (MR).*

Treatment	mg kg^{-1}, i.p.	Food intake (g per rat ± s.e.) Sham operated	MR lesioned
Saline	—	8·5 ± 0·4	9·6 ± 0·9
Quipazine	10	1·4 ± 0·2*	2·1 ± 0·5*

Each value represents the mean of 2 h food intake of 6 animals.
* $P < 0.01$ with respect to saline.

serotoninergic neurons in the brain (Dahlström & Fuxe, 1964).

These findings are compatible with the hypothesis that quipazine may decrease food intake by stimulating directly central 5-HT receptors. Although some controversy exists about the exact role of 5-HT in the regulation of food intake (see review by Baile, 1974), it has been recently shown that injected peripherally (Rezek & Novin, 1975), in the lateral ventricles (Kruk, 1973) or in the hypothalamus (Sharpe & Myers, 1969), it reduces food intake, while the intraventricular injection of *p*-chlorophenylalanine, a strong inhibitor of 5-HT synthesis (Koe & Weissamn, 1966) or 5,7-dihydroxytryptamine, a selective depletor of 5-HT in the central nervous system (Baumgarten & Lachenmayer, 1972), produces an increase of food intake and over-weight (Breisch & Hoebel, 1975; Saller & Stricker, 1976). It has been recently suggested (Samanin & others, 1972; Jespersen & Scheel-Krüger, 1973) that fenfluramine may decrease food intake by interacting with brain 5-HT. In fact, the effect of fenfluramine on food intake is also inhibited by methergoline (Jespersen & Scheel-Krüger, 1973; Garattini & others, 1975b). However, fenfluramine, unlike quipazine, seems to act by releasing 5-HT and by inhibiting its reuptake as shown by experiments *performed* either with blood platelets (Garattini & others, 1975a; Buczko, de Gaetano & Garattini, 1975) or with brain slices (Fuxe, Farnebo & others, 1975), which may explain why the effect of fenfluramine is reduced by a destruction of serotoninergic neurons obtained either by lesions of the nucleus raphé medianus (Samanin & others, 1972) or by an intraventricular injection of 5,6-HT (Clineschmidt, 1973).

Both quipazine and fenfluramine would act by increasing central serotoninergic activity, the former through a direct stimulation of 5-HT receptors, the latter by making more 5-HT available for the receptors. In conclusion, the present data further support the hypothesis for an involvement of central 5-HT in the mechanisms regulating food intake and suggest that quipazine may be an additional useful tool to investigate such mechanisms.

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