ACTION OF GRACIDIN (PHENMETRAZINE) ON RATS WITH "HYPOTHALAMIC" OBESITY

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Phenmetrazine (2-phenyl-3-methyl-tetrahydro-1,4-oxazine)hydrochloride * is a drug depressing appetite and thus of value in the treatment of pathological obesity. The literature at present is based largely on clinical material [2, 4, 5, 8, 12, 15]. A decrease in the body weight (by approximately 5% in 15 days) has also been found in experiments on animals on account of depression of the appetite [16].

It has been suggested that phenmetrazine acts through the central nervous system, namely through the hypothalamus [9], which contains, as experiments on animals have shown, two "centers" regulating the demand for food [3, 7, 13, 14]. This hypothesis concerning the mechanism of action of this drug may be verified experimentally by studying the action of gracidin on rats in which the "satiety" center of the hypothalamus has been destroyed.

EXPERIMENTAL METHOD

Experiments were conducted on 30 female albino rats weighing 180-220 g in which zones of destruction had been produced by means of a stereotaxic apparatus [1] bilaterally in the region of the ventromedial nuclei of the hypothalamus (the "satiety center"), leading to the development of obesity. The animals were subdivided into groups depending on the time elapsing between the operation and the beginning of administration of phenmetrazine: group 1) 1.52 months (the period of intensive gain in weight); and group 2) 3 months, when the animals had attained a considerable degree of obesity and gained comparatively little additional weight.

The Hungarian preparation of phenmetrazine (gracidin) was used. It was given by mouth through a tube twice daily.

Gracidin was given to five rats of each group, and the remaining five with "hypothalamic obesity" served as controls. The drug was given for 2.5-3 months in doses from 2 mg, gradually increased to 15 mg per rat per diem. The animals of group 2 received gracidin for a short period in a daily dose of 20 mg.

The spontaneous activity of the normal animals, the rats with "hypothalamic obesity" and the animals with obesity receiving gracidin was determined in Greenman's revolving chairs, in which every half-turn was recorded on the counter. The animals were placed in the chair 15 min after administration of the preparation for a period of 3 h daily for 4 days. Some rats were kept in the Greenman's chairs for 18 h on alternate days, for four times altogether. The last variant of the experiment is methodically more accurate but it is not so suitable for this type of investigation, for in rats with "hypothalamic obesity" whose food consumption is much greater than normal, prolonged starvation may be reflected significantly in their weight curve.

EXPERIMENTAL RESULTS

On the basis of data in the literature [16] it was decided to give gracidin at first in a dose of 20 mg per rat per diem. The animals reacted to the first doses of the drug with a sharp fall in body weight (Fig. 1) and strong excitation, however, and this dose was clearly too large. Administration of the minimal effective dose of gracidin

*Preludin (Geigy) – Publisher's Note.

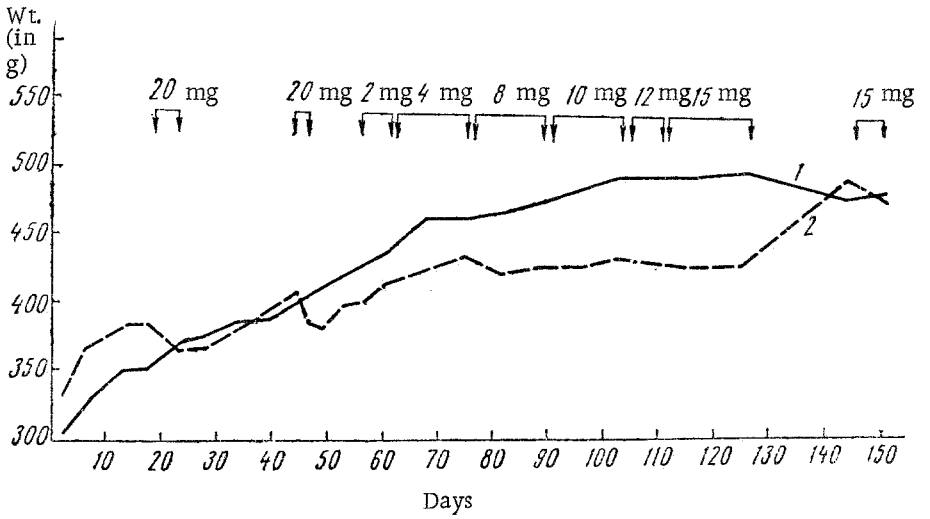

Fig. 1. Action of gracidin on rats with "hypothalamic obesity" 3 months after operation (group 2). 1) Mean weight of 10 control "obese" rats; 2) mean weight of 5 "obese" rats receiving gracidin.

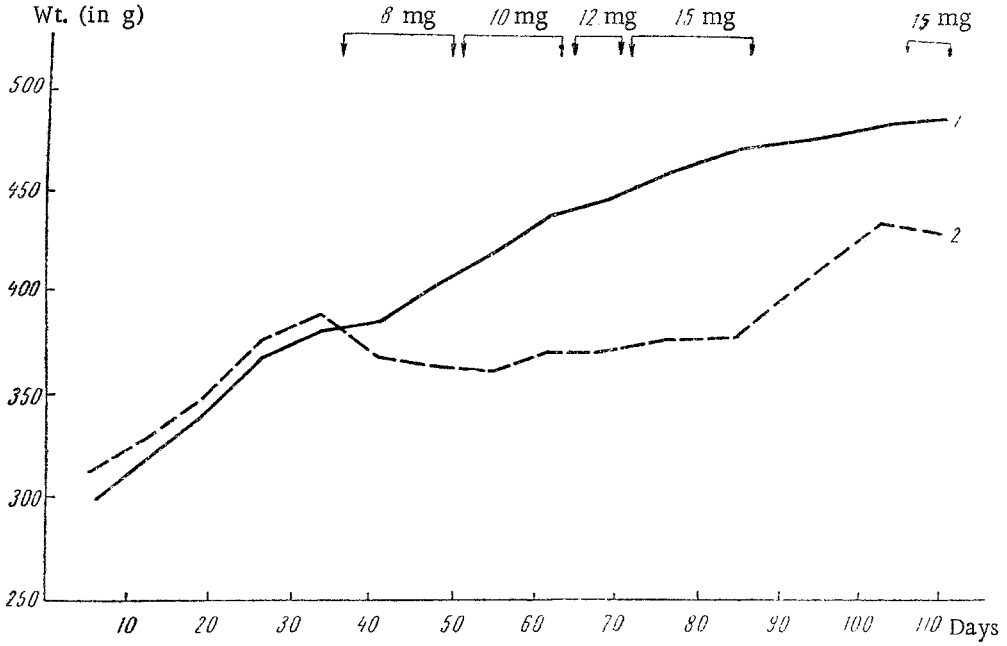

Fig. 2. Action of gracidin on rats with "hypothalamic obesity" 1.5-2 months after operation (group 1). 1) Mean weight of 10 control "obese" rats; 2) mean weight of 5 "obese" rats receiving gracidin.

(8 mg) led to a decrease in the weight of the animals of group 1 in the first week by 6.3% and in the animals of group 2 by 2.6%. The loss of weight of the animals of group 2 then ceased, but in the following 2 weeks the body weight of the animals of group fell by a further 1.4%. A subsequent gradual increase in the dose of the drug (10, 12, 15 mg per rat per diem) caused no further fall in the body weight. A slight increase in weight was actually found, although admittedly it was less than that found in the control "obese" rats.

After prolonged administration of gracidin with a gradual increase in the dose (in group 1 for over 1.5 months, in group 2 for 2.5 months) the animals did not receive the drug for 17 days, which led to a sharp increase in the body weight (by approximately 15%). The rats then were given gracidin again for a week in a dose of 15 mg, which led to a further fall in the weight of the experimental animals (Figs. 1 and 2).

Effect of "Hypothalamic Obesity" and Gracidin on Spontaneous Activity of Rats

Group of animals	No. in group	No. of meas. in group	No. of revolutions of chair per hour (mean data for group)
Normal	4	16	63,4 ± 12,7
"Obese"	9	30	32,6 ± 3,7
"Obese" receiving gracidin	6	24	56,6 ± 6,3

As already mentioned, gracidin in a dose of 20 mg caused very intensive nervous excitation. Within 15 min after administration of the preparation and for several hours thereafter the experimental animals assumed postures of stress and shook their head from side to side repeatedly, as if sniffing. The rats developed marked exophthalmos. When an attempt was made to pick them up, the usually docile animals hissed, jumped, and tore themselves away. For 5-6 h after administration of the preparation, the rats refused to eat. With a gradual increase in the dose from 2 to 15 mg, this intensive nervous excitation was no longer observed. Although this nervous excitation was not of the motor type, it was decided to determine the spontaneous activity of the experimental rats while they were receiving gracidin (see table).

It is clear from the table that the spontaneous activity of the rats with "hypothalamic obesity" was much less than that of the normal animals, in agreement with reports in the literature [6, 11]. The motor activity of the "obese" rats receiving gracidin in a dose of 10-15 mg was almost normal.

Hence, in the rats with "hypothalamic obesity" the suppression of the characteristic tendency towards obesity was observed under the influence of gracidin, although this effect was noted only while the preparation was being given. Consequently, it may be concluded that phenmetrazine does not act through the "satiety center," which was destroyed in these animals, but it evidently inhibits the second "food center" of the hypothalamus, as a result of which the feeling of hunger is diminished and the appetite is reduced.

On the other hand, some degree of habituation to gracidin was clearly seen, for in the experimental conditions used only the first effective dose lead initially to a definite fall in the body weight, and a subsequent increase in the dose did not reduce the body weight. The question of habituation to phenmetrazine has received little attention in the clinical literature. However, reports have been published [10] stating that in the initial period phenmetrazine lowers the body weight more intensively, and its action grows weaker with time.

It may be concluded from this limited material obtained by determining the spontaneous activity that rats with "hypothalamic obesity" and receiving gracidin are slightly more active than control animals with obesity and their motor activity is very similar to that of normal rats.

Comparison of the action of gracidin on the rats of the two groups showed that in the animals of group 1, while still in the stage of intensively gaining weight, the action of the preparation was more marked than in the animals of group 2, showing a small gain in weight compared with the controls (plateau on the curve), and at the end of the experiment a decrease in weight was actually observed.

SUMMARY

Rats with "hypothalamic" adiposity under the influence of the clinical preparation gracidin during a prolonged period (1½-2 months) were found to have an inhibition of the trend toward adiposity characteristic of these animals. This effect, however, was noted only during the period of administration of the preparation. Hence the conclusion that gracidin acts not through the "engorgement center" which is destroyed in these animals but apparently through inhibition of the second, "food center" of the hypothalamus, as a result of which the feeling of hunger and the appetite for food are reduced. Upon a prolonged administration of gracidin a certain habituation to the drug has been noted. The observations also evidence a gradual reduction of the effect of gracidin on the excitability of the animal nervous system.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
