difference between general mean values was assessed by Student's t-test. The difference was considered significant at $p < 0.05$.

Results and discussion. ^{3}H-DHA, a potent β-adrenergic antagonist, has been used to identify β-adrenergic receptors in adipocyte membrane preparations[5]. By using these direct binding methods, the number and affinity (K_D) of ^{3}H-DHA-binding sites in adipocyte membranes from SHR and essentially hypertensive patients and from controls were assessed by regression analysis of Scatchard plots[7]. As shown in the figure, the maximal number of ^{3}H-DHA binding sites in adipocyte membranes from SHR (317 fmoles/mg of protein) was 2-fold more than in membranes from control rats (155 fmoles/mg of protein) ($p < 0.001$). The dissociation constant of ^{3}H-DHA binding in membranes from SHR was 3-fold more than in control membranes. As shown in the table, the maximal number of ^{3}H-DHA binding sites in plasma membranes from hypertensive patients is 1780 fmoles/mg of protein; this exceeds the corresponding value in the normotensive control group (1080 fmoles/mg of protein) by 1.65-fold ($p < 0.05$). K_D in the case of hypertensive patients (8.98 nM) is 2-fold higher than the control dissociation constant (4.72 nM) ($p < 0.05$). Thus, an increase in the maximal binding sites and a decrease in the affinity of β-adrenoceptor to the β-adrenergic antagonist were observed both in hypertensive patients and in SHR. The decrease mentioned above in β-adrenoceptor affinity to ^{3}H-DHA is evidently due to membrane alterations in adipocytes from hypertensive rats and patients. This suggestion is confirmed by the finding of alterations in calcium binding with adipocyte plasma membranes from SHR and hypertensive patients[8]. Earlier it was reported that the erythrocyte and smooth muscle membranes are altered in these types of hypertension[9-11]. Therefore, the newly observed decrease in β-adrenoceptor affinity again confirms the hypothesis of a widespread membrane alteration in essential hypertension. It is difficult to explain at present the role of alteration in β-adrenergic receptor properties of adipocytes in the types of hypertension considered. Nevertheless, it evidently reflects some features of the interaction between catecholamines and β-adrenoceptors in hypertension.

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3 Yu.V. Postnov, S.N. Orlov, M.B. Reznikova and N.I. Pokudin, Pflügers Arch. *384*, 183 (1980).
4 M. Rodbell, J. biol. Chem. *239*, 375 (1964).
5 L.T. Williams, L. Jarett and R.J. Lefkowitz, J. biol. Chem. *251*, 3096 (1976).
6 O.H. Lowry, N.J. Rosenbrough, A.L. Farr and R.I. Randall, J. biol. Chem. *183*, 265 (1951).
7 G. Scatchard, Ann. N.Y. Acad. Sci. *51*, 660 (1949).
8 Yu.V. Postnov and S.N. Orlov, Pflügers Arch. *385*, 85 (1980).
9 A.W. Jones, Circulation Res. *5*, 563 (1973).
10 Yu.V. Postnov, S.N. Orlov and A.S. Shevchenko, Cardiology, Moscow *15*, 88 (1975).
11 G.M. Boriskina, P.V. Gulak and Yu.V. Postnov, Experientia *34*, 744 (1978).

Inhibition of food intake in the rat by cyproheptadine

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Summary. In a model of conditioned feeding behavior, oral administration of cyproheptadine (1–100 mg/kg), 30 min before presentation of food, produced a dose-dependent reduction of food intake in the rat ($ED_{50} \simeq 17$ mg/kg during the 1st h of testing). This anorexic effect persisted for at least 24 h. These results provide further evidence that under certain conditions cyproheptadine, which is used as an orectic agent in man, can produce anorexia.

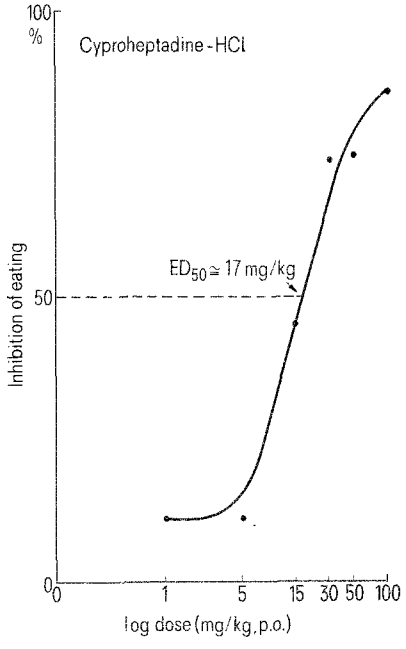
Cyproheptadine (5-[1-methyl-piperidylidene-(4)]-5H-dibenzo-[a,d]-cycloheptane), a tricyclic antiserotonin-antihistaminic drug, stimulates appetite and produces an increase in body weight in man[2-7]. However, the evidence for such an action of cyproheptadine in rats is not so clear. For example, Lavenstein and coworkers[4] and Bergen[2] did not observe appetite-stimulating effects of this agent in rats, whereas Baxter and coworkers[8] and Oomura and colleagues[9] reported that it produced an increase in food intake in rats. Opitz and colleagues[10] found that cyproheptadine, given orally or i.p. (1–40 mg/kg), had no effect or could produce anorexia in the rat, but for the 1st 2 h after s.c. administration (12.5 mg/kg) it increased food intake in fasted animals. However, s.c.-administered cyproheptadine (7 or 20 mg/kg) did not have an appetite-stimulating effect in fasted rats that had been trained to bar-press for food, and at the higher dose the drug could produce an anorexigenic effect[11]. Due to these conflicting results, we decided to conduct further studies on the effect of cyproheptadine on feeding behavior in the rat.

Male Sprague-Dawley rats (Charles River), 180–215 g, were housed individually in plastic cages ($14 \times 20 \times 30$ cm) containing litter. They were allowed to acclimatize to their new surroundings for a week, with food and water ad libitum[12], and were subjected to a daily rhythm of 12 h of darkness (19.00–7.00 h) and 12 h of light (7.00–19.00 h). The animals were conditioned to consume food between 11.00 and 15.00 h[13], while having free access to water; they received their cups of food in plastic cages ($8.5 \times 13 \times 27$ cm). Food consisting of a mixture of 600 g of powdered standard rat chow (Union d'Alimentation Rationnelle) and 250 ml of soybean oil was given to the rats daily. The amount of food consumed was determined by weighing the cups before and at 1 h and 4 h after their presentation to the animals. The rats consumed 12.9 ± 0.5 g of food during the 1st h and 15.8 ± 0.4 g of food in the total 4-h test period (means $\pm$ SEM of 36 values from 6 rats in both cases). The criterion for stability of food intake was considered to have been met when the quantity consumed did not vary more than 5 g/day per animal. Determinations made on Tuesday and Wednesday were considered as control values, drugs were tested on Thursday, and determinations made on Friday permitted evaluation of sustained effects of the drug. Determinations made on Monday were not used since the animals had received 2 pellets of standard rat chow on Saturday and Sunday. Animals were tested in groups of 6. Cyproheptadine-HCl (Merck) was administered orally in a dose range of 1–100 mg/kg

Effect of orally-administered cyproheptadine on food intake in the rat

Dose of cyproheptadine (mg/kg, p.o.)	Food consumption (g) During 1st h			During 4 h		
	Control days[a]	Day of drug	Day after drug	Control days[a]	Day of drug	Day after drug
1	13.4±1.0	11.9±0.9	11.1±1.9	15.8±0.7	15.4±1.2	12.3±1.9
5	11.2±1.1	10.0±1.9	9.8±1.5	14.6±1.1	12.4±1.8	13.4±1.5
15	13.0±0.7	7.1±0.8[d]	9.7±1.2[b]	15.3±0.5	11.7±1.2[b]	13.3±1.7
30	12.2±0.9	3.2±0.5[d]	6.7±1.9[b]	16.4±0.9	10.3±1.2[c]	10.7±2.4[b]
50	13.1±0.7	3.3±0.8[d]	5.5±0.9[d]	16.2±1.1	6.4±1.1[d]	9.8±2.4[b]
100	14.3±1.9	2.0±0.6[d]	3.5±0.5[d]	16.7±1.2	7.0±1.7[d]	7.1±1.0[d]

[a] Control days refers to values obtained during the 2 days prior to cyproheptadine administration. Means±SEM of 12 values from 6 animals for control days and of 6 values from the same 6 animals for other days; [b,c,d] indicate, respectively, $p < 0.05$, $p < 0.01$ and $p < 0.001$ for comparisons between these values and corresponding 'control' values; Student's t-test (2-tailed).



Inhibition of food intake by orally-administered cyproheptadine. Values were calculated from those obtained for food intake during the 1st h of testing (see table).

(1.0 ml/100 g b.wt) on Thursday, the vehicle (water) being administered on the other days. Each animal received the different doses in a random order 30 min before presentation of food; all doses were represented on each test day.

Orally-administered cyproheptadine produced a dose-dependent decrease in food intake which was evident after 1 h and after 4 h of testing, and which persisted until the following day (table). This effect of cyproheptadine occurred with an $ED_{50} \simeq$ mg/kg (fig. 1), a value which can be compared with those of other drugs tested orally using the same experimental design; *d*-amphetamine-SO_4 ($ED_{50} \simeq 0.4$ mg/kg), fenfluramine-HCl ($ED_{50} \simeq 1.0$ mg/kg), the GABA-agonist THIP ($ED_{50} \simeq 4$ mg/kg)[14,15]. The sustained anorexigenic effect of cyproheptadine seems especially noteworthy since such an effect was not produced by *d*-amphetamine, fenfluramine or THIP. Over the dose range used (1–100 mg/kg), cyproheptadine did not produce drowsiness or motor deficit in the animals, in contrast to the finding of Chakrabarty and coworkers[11] that s.c.-administered cyproheptadine (20 mg/kg) produced drowsiness in rats.

From these results it becomes readily apparent that the 'appetite-stimulating' drug cyproheptadine can, under certain conditions, produce a pronounced inhibition of food intake in the rat. This finding adds support to previous studies which showed that oral, i.p.[10] or s.c.[11] administration of cyproheptadine can produce anorexia in the rat. The reason why cyproheptadine produces anorexia in rats while serving as an effective orectic agent in man might be related to a species difference[10]; i.e., the metabolic handling and/or absorption of the drug might differ. However, several other factors might also contribute to this difference as well as to the differences obtained in experiments with rats by different investigators. Such factors include: test environment; mode of drug administration (acute or chronic); test used for determining food intake; condition of test animals (e.g., fasted or non-fasted). Also, it should be noted that cyproheptadine does not only act as a serotonin-antagonist; this agent can cantagonize histamine (H_1)-receptors[16], and dopamine-receptors[17], and it can influence the secretion of insulin and growth hormone[18,19]. In addition to revealing further the complexity of feeding behavior, these results indicate that drugs which produce either anorexic or orectic responses in rats should be examined for their possible anorectic or orectic activity in man.

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2 S.S. Bergen, Am. J. Dis. Childh. *108*, 270 (1964).
3 F. Francini, J.C. Santana and J. Kitrosen, Prensa med. argent *54*, 826 (1967).
4 A.F. Lavenstein, F.P. Decaney, L. Lasagna and T.E. Van Metre, J. Am. med. Ass. *180*, 912 (1962).
5 D.P. Mertz, Germ. med. Mon. *15*, 484 (1970).
6 R.E. Noble, J. Am. med. Ass. *209*, 2054 (1969).
7 T.E. Van Metre, Jr, Sth. med. J. *55*, 1305 (1962).
8 M.G. Baxter, A.A. Miller and F.E. Soroko, Br. J. Pharmac. *39*, 229P (1970).
9 Y. Oomura, T. Ono, M. Sugimori and T. Nakamura, Pharmac. Biochem. Behav. *1*, 449 (1973).
10 K. Opitz, M.L. Weischer and L. Klose, Arzneimittel-Forsch. *21*, 957 (1971).
11 A.S. Chakrabarty, O.P. Bhatnagar and K. Chakrabarty, Indian J. med. Res. *62*, 726 (1974).
12 T.G. Heffner, M.S. Zigmond and E.M. Stricker, J. Pharmac. exp. Ther. *210*, 386 (1977).
13 J.T. Oliver, Archs int. Pharmacodyn. *211*, 253 (1974).
14 N. Blavet, F.V. DeFeudis and F. Clostre, Gen. Pharmac., in press (1981).
15 N. Blavet, F.V. DeFeudis and F. Clostre, J. neural Behav. Biol., in press (1981).
16 C.A. Stone, H.C. Wenger, C.T. Ludden, I.M. Stavorski and C.A. Ross, J. Pharmac. exp. Ther. *131*, 73 (1961).
17 J.-C. Gilbert and L.I. Goldberg, J. Pharmac. exp. Ther. *193*, 435 (1975).
18 J.A. Baldridge, K.E. Quickel, J.M. Feldman and H.E. Lebovitz, Diabetes *23*, 21 (1974).
19 K.L. Hintze, A.B. Grow and L.J. Fischer, Biochem. Pharmac. *26*, 2021 (1977).