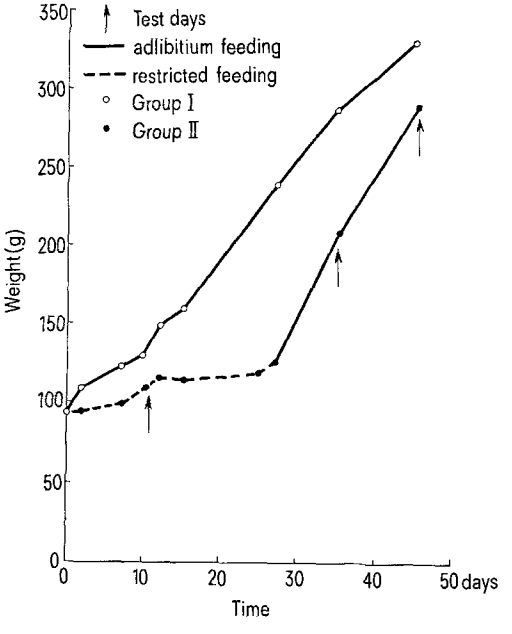
The Feeding Response to β-Adrenergic Active Agents During Induced Compensatory Growth in Rats

The antagonistic effects of α and β-adrenergically coded hypothalamic neurons on feeding behaviour has now been well documented for the rat (LEIBOWITZ[1]). The possibility that the natural hyperphagia observed in young growing animals could be due to functional immaturity in the so-called 'β satiety system', comparable to the amphetamine-induced anorexia, and insulin hyperphagia reported by LYTLE, MOORCROFT and CAMPBELL[2] was investigated by MOBERG, CLARKE and ROBINSON[3]. The present experiment was designed to examine the sensitivity of these systems during induced compensatory growth.

40 female, 5-week-old Sprague-Dawley rats were divided into 2 groups. Group I was fed standard lab chow ad libitum and grew normally throughout the experiment which lasted for 45 days. Group II was restricted to an intake which permitted a growth of less than 2 g/day for the first 4 weeks of the experiment, but thereafter they were fed ad libitum, and grew at a rate of over 8 g/day. This compared with the mean growth rate of 5 g/day for the rats in Group I. Food was removed at 15.00 h from all rats, 23 h prior to injection of drugs. The drugs were administered i.p., in all cases at doses of 10 mg/kg body weight, since similar responses are evoked by either intraperitoneal or intrahypothalamic injection (GOLDMAN, LEHR and FRIEDMAN[4]). 1 h after injection the rats were fed and intake recorded for the 2 h later following feeding. 3 drug tests were conducted on days 11, 35 and 45 following the commencement of the experiment. For the Group II rats, the days of drug tests corresponded to periods when they were restricted (day 11), making compensatory growth (day 35) and essential back to normal (day 45) (see Figure). Between each test, rats within each group were re-randomized and allocated to a different treatment at the next test.



Growth curves of adlibitium fed and restricted – adlibitium fed rats.

Analysis of variance was used according to a $4 \times 3 \times 2$ factorial design, the factors being 4 drug treatments, 3 ages, and 2 feeding regimens following SNEDECOR[5]. Two separate analyses were carried out; in the first the food intake of water-treated Group I rats was considered to be 100%, and the intake of Group II rats expressed accordingly. In the second, the food intake of water-treated Group II rats was considered to be 100% and drug treatments within this group expressed accordingly. In this way, from the Table, both the actual increase in food intake of Group II rats can be seen, as well as the relative effects of the drugs. Both groups weighed 92 g at the start of the experiment (day 0). At 27 days of age the Group II rats mean weight was only 57% of the Group I rats (240 g), but following ad libitum feeding from 27 to 45 days the weight of Group II rats recovered to the point where it was some 85% of that of Group I by day 45, which is a clear demonstration of compensatory growth (see Figure).

Food intake data for the 2 h period following feeding are presented in the Table. The data show that at day 11 the restricted Group II rats, when offered ad libitum access to food for 2 h, consumed about twice as much as

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[2] K. D. LYTLE, L. H. MOORCROFT and B. A. CAMPBELL, J. comp. Physiol. Psychol. *77*, 388 (1971).
[3] G. P. MOBERG, C. R. CLARKE and D. W. ROBINSON, Br. vet. J. *129*, 27 (1973).
[4] H. N. GOLDMAN, D. LEHR and E. FRIEDMAN, Nature, Lond. *231*, 453 (1971).
[5] G. W. SNEDECOR, *Statistical Methods* (Iowa State College Press, Ames, Iowa, USA 1959).

The feeding response to β-adrenergic active agents on 3 occasions in rats growing at different rates

Injection treatment	Day 11			Day 35			Day 45		
	[1]Group I	[1]Group II	[2]Group II	[1]Group I	[1]Group II	[2]Group II	[1]Group I	[1]Group II	[2]Group II
Water	100[a]	183[c]	100[a]	100[a]	134[b]	100[a]	100[a]	142[b]	100[a]
Propanolol (P)	81[a,b,c]	165[c]	98[a]	140[b]	126[b,a]	111[a]	134[b]	133[b]	99[a]
Isoproterenol (I)	60[c]	153[d]	83[a]	19[c]	19[c]	13[c]	24[c]	32[c]	23[c]
I+P	74[b,c]	159[d]	89[a]	118[a,b]	104[a]	91[a]	76[d]	107[a]	80[a,d]

[1] All data are expressed as percentages, where the water treated Group I animal's mean intake = 100%. Values with the same superscripts to Group I are not significantly different $P < 0.05$. [2] These values are expressed as percentages, where the water treated Group II rats = 100%.

the Group I rats regardless of drug treatment (Table, columns 1 and 2). However, there was no significant difference within Group II rats between any of the drug treatments and the control (distilled water) rats. Group I rats, however, did show a significant ($P < 0.01$) depression in food intake when injected with isoproterenol (Table, column 1). Propranolol injected with isoproterenol was unable to restore food intake in Group I rats at 11 days, and propranolol injected alone had no significant effect on either Group I or Group II rats at 11 days.

At 35 days, Group II rats were making a rapid compensatory growth. Drug injections at 35 days demonstrated that both Group I and II rats had significantly ($P < 0.001$) depressed food intake when injected with isoproterenol (Table, columns 4 and 5), and that intake was restored to normal by propranolol injected with Isoproterenol. There was no significant difference with any drug treatment between the Group I and II rats, although Group II controls still showed a higher food intake. Propranolol in both groups elevated intake and in Group I significantly so ($P < 0.01$).

At 45 days, an identical pattern of response to that seen at 35 days was observed. All the differences in Group I animals (Table, column 7) were significantly different from each other at the $P < 0.05$ level of probability and in the case of the isoproterenol treatment at the $P < 0.001$ level from the control and propranolol treated rats.

The results support the conclusion of MOBERG et al.[3] that there is a functional immaturity in the young with respect to the 'β adrenergic satiety system' proposed by LEIBOWITZ[1], as seen by the increasing inhibition of food intake by isoproterenol with advancing age in both groups of rats.

In the present experiment, there appears to be an increased response to the β antagonist, propranolol, with advancing age which may also be supporting evidence of a delayed maturity of the β system which in turn may account for the hyperphagia seen in young, growing animals. KENNEDY[6], for example, has shown that ventromedial hypothalamic lesions in the young do not induce hyperphagia as easily or to the same extent as in older animals.

The results do not, however, support the hypothesis that animals which are naturally hyperphagic, namely those demonstrating active compensatory growth in this experiment, as opposed to those with surgically or pharmacologically induced hyperphagia, have a depressed β satiety activity. Only during actual restriction were isoproterenol treated rats significantly different between Groups I and II ($P < 0.05$). Whereas, during compensatory growth itself the response to isoproterenol between the Groups I and II was identical.

Résumé. Des drogues dites β adrénergiques et pourvues d'activité agoniste et antagoniste furent injectées à des rats à jeun et préalablement soumis à un programme de croissance normale, restreinte ou compensatrice afin de vérifier durant l'hyperphagie induite naturellement il y a suppression dans la sensitivité du système de satiété dit β. Les résultats obtenus ne soutinrent pas une telle hypothèse, cependant confirmèrent l'immaturité fonctionnelle apparente du système chez les jeunes animaux, objet d'une précédente publication.

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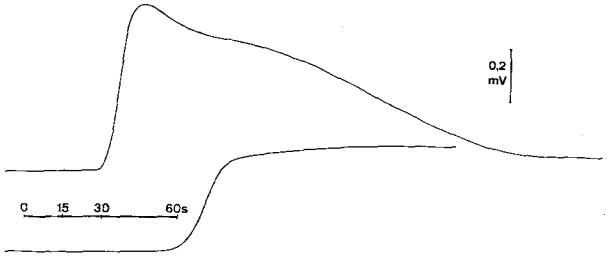
[6] G. C. KENNEDY, J. Endocr. *16*, 9 (1957).

Nachweis des Azid-Potentials an der isolierten Kaninchennetzhaut

Im Jahre 1952 zeigte NOELL[1] erstmals, dass i.v. oder i.a. Injektion von Azid am Kaninchen ein mehrere mV hohes corneapositives Potential auslöst. Dieser Azideffekt wurde mit dem Pigmentepithel in Zusammenhang gebracht, besonders da nachgewiesen wurde, dass er durch selektive Schädigung des Pigmentepithels (Jodatvergiftung) nahezu vollständig ausgeschaltet werden konnte und dass die Substanz eine Erhöhung von Bestandpotential und c-Welle bewirkte (NOELL[2]). Substanzen, die zu einer Reduktion der c-Wellen-Amplitude führten, wurden in ihrem Effekt durch Verabreichung von Azid abgeschwächt (HOMMER et al.[3]). Ziel der vorliegenden Untersuchung war es, die Frage zu überprüfen, ob und in welchem Ausmass retinale Komponenten bei der Entstehung des Azideffektes beteiligt sind. Zu diesem Zweck wurde Azid der Nährlösung für die isolierte pigmentepithelfreie Netzhaut zugesetzt.



Azidpotentiale einer isolierten umströmten Kaninchennetzhaut. Dem Nährmedium wurde im Zeitpunkt 0 je 20 mg Azid beigefügt und zwar entweder durch Injektion in den zuführenden Schlauch (obere Kurve) oder durch Zugiessen in das Vorratsgefäss (Menge des Mediums je 100 ml). Endkonzentration in dem verwendeten Nährmedium betrug daher jeweils 3 mM/l. Näheres siehe Text.

Methodik. Die Untersuchungen wurden an 10 Netzhäuten durchgeführt, die aus dunkeladaptierten Kaninchenbulbi unter sorgfältiger Entfernung des Pigmentepithels herauspräpariert worden waren. Die Technik der Präparation und Potentialableitung mit Hilfe von Ag-AgCl Elektroden über Agarbrücken wurde bereits früher ausführlich beschrieben[4]. Azid wurde in Form einer Lösung von NaN_3 entweder dem Gesamtnährmedium zu-

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[2] W. K. NOELL, Project Report 21-1201-0004 No 1, USA Air Force School of Aviation Medicine, Randolph Field, Texas (1953).
[3] K. HOMMER, W. D. ULRICH und L. WÜNDSCH, v. Graefes Arch. klin. exp. Ophthal. *175*, 121 (1968).
[4] W. SICKEL, H. G. LIPPMANN, W. HASCHKE und CH. BAUMANN, Dt. ophthal. Ges. *63*, 316 (1961). – R. HANITZSCH und A. L. BYSOV, Vision Res. *3*, 207 (1963). – R. HANITZSCH und H. BORNSCHEIN, Experientia *21*, 484 (1965); A. v. LÜTZOW, Experientia *22*, 215 (1966).