birds seem to be crucial components of their timekeeping machinery, but major differences may exist between them (for example, pinealectomized birds are arrhythmic in DD whereas pinealectomized lizards are not). There is strong evidence that the avian pineal is the site of a master driving oscillator; the data presented here show that the lizard pineal is also an important component of circadian organization, but its exact function and the routes by which it is coupled to other components of the circadian system await elucidation.

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19 August 1976; revised 26 October 1976

Intravenous Self-Feeding: Long-Term Regulation of Energy Balance in Rats

Abstract. *Rats learned to press a lever for intravenous self-injection of liquid diet during periods of several weeks when oral food was not available. The intakes were low but regulated, and were sufficient to balance energy expenditures at low body weight. Systemic receptors alone are thus adequate to motivate feeding behavior and meter the caloric yield of the intravenous injections.*

The frequency of meals and their size together determine the daily food intake of animals. We do not fully understand the physiological states which generate these meal patterns, yet such information would considerably aid appetite control programs. When an animal begins to feed there is a decline of intracellular energy production (from all fuel sources) below a critical level (*1*, *2*). Sensory incentives, such as taste, have a modulating and sometimes overriding influence on these energy factors. The determinants of meal size are also complex, involving conditioned and unconditioned factors at peripheral (oral and gastric) as well as duodenal and systemic levels (*3*).

We have studied the capacity of systemic receptors alone to motivate and sustain ingestive behavior in rats (*4*). The participation of taste and other orogastric factors was eliminated by allowing the animals to feed themselves intravenously. We now report the characteristics of the long-term regulation of ingestion so achieved.

Adult male rats were fitted with permanently implanted intravenous (auricular) catheters. Our surgical preparation and infusion apparatus, described elsewhere (*5*), allows the animals complete freedom of movement. After a few days of postoperative recovery, the rats were deprived of oral food and given access to a lever which was positioned outside a window in the cage wall (in order to minimize accidental presses). Relays and timers caused each press on the lever to activate an infusion pump and deliver through the catheter a known amount of nutritive fluid from a 50-ml syringe. Several types of fluid were used, all of a concentration about 1.0 kcal/ml and containing most of the nutrient requirements of the rat (*2*, *6*). Water was freely available, but intakes were low despite the hypertonicity of the self-injected fluids.

The present results were obtained from 30 rats that did not develop pathological or other problems such as leaks in the infusion line. These rats were studied for 5 to 30 consecutive days. Although they had had no prior experience with levers, some 70 percent of them self-administered a fairly constant amount of nutritive fluid from day 2 or day 3 of the experiment. The remaining 30 percent of the rats showed little spontaneous pressing, and had to be attracted to the bar by placing a few drops of sweet fluid on it. Operant responding was immediately initiated, and no further oral incentives were given. Thereafter, all of the rats deliberately activated the infusion pump with a single press of the lever. Most rats were placid or groomed a little during injections, but three animals consistently chewed the lever. After steady responding was established, the daily intakes were 27 kcal per 24 hours (range, 15 to 50 kcal); no arbitrary "learning criterion" was applied. Presses of the lever were distributed throughout the 24 hours, with the highest density occurring around nightfall (Fig. 1). This corresponds to the time of maximal locomotor activity, hence of energy expenditure. In terms of calories, the amount received by each rat per injection (quantum) was most usually

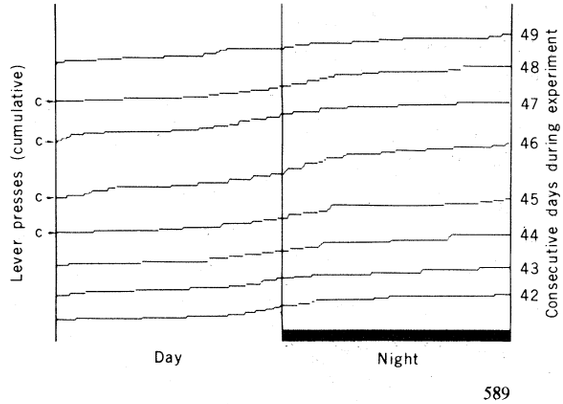

Fig. 1. Cumulative record (expressed as lever presses) of intravenous self-feeding in rat 178 on consecutive days. The concentration (*c*) of the infused fluid was halved on days 45 to 48, with an average increase of 40 percent in the volume injected.

Table 1. Experimental manipulations of intravenous self-feeding. The continuous infusion of four rats (two with lipids, two with glucose and amino acids) causes a rapid reduction in the amount of fluid that is self-injected. The programmed infusions were continued for 2 to 4 days of which the first two are indicated. Data from the first day without continuous supplement are shown in the line for recovery. Note the slight lag in decrease and recovery of intravenous intakes. A decrease ($N = 7$) or increase ($N = 2$) of injected quantum through a twofold change of infusion rate caused no change in the calories self-injected. The effects were immediate and persisted for the 2 to 5 days of modified quantum, returning to baseline on the first day of recovery. In all cases the range was ± 30 percent of the indicated mean.

Day	Experiment	Intravenous feeding ($N = 4$)*			Quantum change ($N = 9$)†	
		Continuous infusion (kcal)	Self-intake (kcal)	Change in body weight (g)	Intravenous self-intake (kcal)	Change in body weight (g)
1	Baseline	0	32		34	
2	Baseline	0	31	−1.5	36	−1.7
3	Supplement	32	8‡	+0.3	34	−1.0
4	Supplement	32	2‡§	−1.3	32	+1.0
5	(or later) Recovery	0	27	−6.7	35	−0.5

*The infusion mixture consisted of lipid for two of the rats and glucose and amino acid mixture for the other two. †The amount of fluid injected (quantum size, in kilocalories) was halved (in seven rats) or doubled (in two rats on days 3 and 4). ‡Reduced from baseline in all four rats. §Day 2 < day 1 in all four rats.

fixed at 1.5 to 2.0 kcal, infused at a rate of 0.4 to 1.0 ml/min; it proved difficult to establish or maintain the rats' responding with quanta below 1 kcal.

The low daily caloric intake, only some 30 percent of the free-feeding oral intake of adult rats, was insufficient to maintain normal energy balance, and body weight fell in a negatively accelerated manner for 1 to 2 weeks. The weight then restabilized at 60 to 80 percent of the original and was thereafter maintained for up to 3 weeks. This stabilization, together with the temporal pattern of intake which seemed to parallel current energy expenditures, suggests that a new level of energy regulation is attained at which both caloric intakes and outputs are reduced; technical reasons alone (most rats eventually developed endocarditis) seem to limit the duration of this regulation.

If this formulation is correct, the new level or "set point" (*7*), which may be a characteristic of the regulatory capacity of unassisted systemic receptors, should be defended against perturbation. As a partial test we assessed the rats' abilities to defend against further weight loss in two ways. First, ten rats were starved to 70 percent of their normal weight before being allowed to feed themselves intravenously. When they were placed on the infusion regime only, little or no further weight loss occurred and such rats stabilized at the same levels as animals which had been responding throughout the 1- to 2-week period of weight loss. Second, four rats which had already stabilized at about 70 percent of their body weight were deprived of the lever for 24 hours, this leading to additional weight loss. When the lever was restored each of the rats pressed the lever two to four times within the first 30 minutes, and the 24-hour intakes were elevated by some 50 percent over the next 2 days, during which time body weight returned (from below) to the stable 70 percent level. Conversely, three rats subjected to a second intravenous self-feeding period (following several days oral feeding during which time operant behavior ceased) once again lost weight to the same 70 percent level as before.

These results indicate that the lowered equilibrium level is defended, presumably through accurate systemic metering of energy inputs and outputs. To further investigate the accuracy of the metering of intravenous inputs we determined the effect of programmed intravenous infusions on the self-initiated intravenous intake. When the same diet was infused continuously throughout the 24 hours in amounts equivalent to the self-administered intake (without continuous infusion) presses of the lever were greatly reduced in number within a few hours (Table 1). The reduction of self-initiated feeding during intravenous loading was almost calorie-for-calorie. This constitutes strong evidence for active metering at the systemic level, and suggests that the operant response is directly controlled by that metering.

A further test of the accuracy of the metering of intravenous intake was provided in experiments in which the quantum delivered per press of the lever was altered. Data in Table 1 indicate that doubling (or halving) the rate of injection (and hence the quantum size in kilocalories) led to an immediate and exact compensation in the operant behavior such that caloric intake remained constant. In other experiments the duration of injection and concentration of the infused fluid were altered. In all cases the rate at which the lever was pressed (per 24 hours) was modified in the direction required to maintain constancy of caloric intake. Such modifications were, however, less adequate or precise than is typical for oral feeding (*4*). In particular, when the nutritive fluid was diluted twofold the self-injected amounts increased by only about 50 percent.

These results are the first indication that systemic sensors, unsupported by oral and gastrointestinal mechanisms, may be adequate to ensure long-term regulation of energy balance. However, the considerable differences between the mode of regulation during intravenous feeding only and that observed with oral feeding attest to the importance of peripheral factors in the etiology of normal and excessive eating. Factors such as taste and texture, and ingestion-linked triggering of hormonal release for fat storage (*8*), undoubtedly influence energy regulation by facilitating the ingestion and subsequent storage of metabolic fuels. Stress appears to enhance reactivity to food stimuli, with consequent overeating of attractive foods by rats and men (*9*). Our parallel studies of intravenous self-administrations of water (*10*) have generated similar conclusions about the importance of both systemic (homeostatic) and peripheral factors in the regulation of ingestive behavior.

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7. Body weight is a convenient index of energy balance, but we do not imply it is a regulated variable. The intravenous intakes were controlled almost immediately despite considerable weight loss for the first 1 to 2 weeks, and decreasing weight did not significantly augment the intake. Set point concepts for body weight are unnecessary here, as elsewhere [for example, Booth (*3*); J. W. Peck, in *Hunger—Basic Mechanisms and Clinical Implications*, D. Novin, W. Wyrwicka, G. Bray, Eds. (Raven, New York, 1976), pp. 297–311].
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3 August 1976; revised 1 October 1976

Evolution in a Time-Varying Environment

Abstract. *A simple model of competition in a time-varying environment was developed and used to discuss the evolution of life-history strategies.*

The concept of r and K strategies has been popular with ecologists for some time (*1–6*). The concept dates to a suggestion by Dobzhansky (*1*) that populations in frequently disturbed environments will tend to have higher maximum rates of increase r than will populations whose densities are more nearly constant. Conversely, MacArthur (*2*) showed that in undisturbed environments phenotypes which can maintain denser equilibrium populations (that is, those with higher "carrying capacities" K) will be selectively favored. The idea that species can be classified in terms of their positions along an r-K continuum was first proposed by MacArthur and Wilson (*3*). This idea has since become the subject of considerable debate (*4–8*).

We first develop a simple model of competition in a time-varying environment. This model extends the Volterra (*9*) competitive exclusion proof to a certain class of time-dependent environments (*10*). We then use this model in discussing the utility of r-K theory (*3–6*).

Consider a set of m populations growing according to the equations

$$\frac{1}{N_i}\frac{dN_i}{dt} = r_i - \gamma_i F(N_1,\ldots,N_m) - f_i(t) \quad (1)$$

for $i = 1,\ldots,m$. Here N_i is the density of population (haploid phenotype) i, r_i is its maximum rate of increase, γ_i is a positive constant, and t is time. All species are limited by the same "limiting factor" $F(N_1,\ldots,N_m)$ (*11*). The function $F(N_1,\ldots,N_m)$ is assumed to be an increasing function of the N_i, with $F(0,\ldots,0) = 0$. The function $F(N_1,\ldots,N_m)$ summarizes the effects of population densities on population growth rates; the values of the γ_i reflect the sensitivities of the various phenotypes to these density effects. The functions $f_i(t)$ are externally imposed, time-varying rates of density-independent mortality (*12*).

We inquire as to which phenotype is most fit. In other words, we ask: After a long time has elapsed (mathematically, as $t \to \infty$), will one phenotype come to predominate? And if so, which one?

A straightforward extension of the Volterra (*9*) competitive exclusion proof yields the answer. Consider two phenotypes growing according to Eq. 1, which can be rearranged as

$$\frac{1}{\gamma_1}\left[\frac{1}{N_1}\frac{dN_1}{dt} - r_1 + f_1(t)\right] = -F(N_1,\ldots,N_m)$$

$$\frac{1}{\gamma_2}\left[\frac{1}{N_2}\frac{dN_2}{dt} - r_2 + f_2(t)\right] = -F(N_1,\ldots,N_m) \quad (2)$$

Since the right-hand sides of these equations are equal, Eq. 2 can be combined and rearranged to yield

$$\frac{dN_1}{\gamma_1 N_1} - \frac{dN_2}{\gamma_2 N_2} = \{[r_1 - f_1(t)]/\gamma_1 - [r_2 - f_2(t)]/\gamma_2\}\,dt$$

integration of which from time 0 to time τ yields

$$\frac{N_1^{1/\gamma_1}(\tau)}{N_2^{1/\gamma_2}(\tau)} = \frac{N_1^{1/\gamma_1}(0)}{N_2^{1/\gamma_2}(0)} \times \exp\left\{\left[r_1 - \frac{1}{\tau}\int_0^\tau f_1(t)dt\right]/\gamma_1 - \left[r_2 - \frac{1}{\tau}\int_0^\tau f_2(t)dt\right]/\gamma_2\right\}\tau \quad (3)$$

We now define the average values $\bar{f}_i$ of the removal functions $f_i(t)$ by

$$\bar{f}_i \equiv \lim_{\tau\to\infty}\frac{1}{\tau}\int_0^\tau f_i(t)dt \quad (4)$$

If the removal function is periodic, $\bar{f}_i$ is the average value of this function over one time period. Alternatively, if $f_i(t)$ is determined by some stochastic process, then $\bar{f}_i$ is viewed as the expected value of $f_i(t)$ over a randomly chosen interval (or at a randomly chosen point). In any case, we assume that the limits in Eq. 4 are well defined.

Substituting Eq. 4 into Eq. 3, we find that as $\tau \to \infty$

$$N_1^{1/\gamma_1}/N_2^{1/\gamma_2} \to \infty$$

if

$$(r_1 - \bar{f}_1)/\gamma_1 > (r_2 - \bar{f}_2)/\gamma_2$$

and

$$N_1^{1/\gamma_1}/N_2^{1/\gamma_2} \to 0$$

if

$$(r_1 - \bar{f}_1)/\gamma_1 < (r_2 - \bar{f}_2)/\gamma_2$$

The proof is extended to include all phenotypes by considering them pairwise (*9*). As $\tau \to \infty$, that phenotype with the largest value of

$$(r_i - \bar{f}_i)/\gamma_i \quad (5)$$

will become infinitely more common than any other phenotype. Since the total density of all phenotypes must remain finite, only the most favored phenotype will be retained at substantial densities (provided $r_i > \bar{f}_i$ and $N_i(0) \neq 0$ for that phenotype); all other phenotypes must approach extinction (*13, 14*).

Equation 5 provides a useful focus for discussing the utility of r-K theory (*3–6*). We first identify

$$F(N_1,\ldots,N_m) = \sum_{i=1}^{m} N_i$$

the total density of all phenotypes, and $\gamma_i = r_i/K_i$, where K_i is the carrying capacity of phenotype i (*15*). With this identification, which transforms Eq. 1 into time-dependent logistic equations (*2, 3*), we see from Eq. 5 that the phenotype with the largest value of

$$K_i(1 - \bar{f}_i/r_i) \quad (6)$$

will replace all others.

Assume now that the various phenotypes do not differ in their susceptibility to externally imposed mortality, so that $\bar{f}_i = \bar{f}$ for all i. Assume further that there exists some trade-off between the ability to reproduce at high population densities and the ability to reproduce at low densities. That is, assume that if phenotype A has higher fitness than phenotype B in one density range, then A will be less fit than B in the opposite density range. As a concrete example, let the admissible pairs of values of r_i and K_i for the various phenotypes lie on the line defined by

$$r_i/r_{\max} + K_i/K_{\max} = 1$$

where $r_{\max}$ and $K_{\max}$ are the largest possible values of r_i and K_i, respectively. In