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The hypothalamic ^{14}C differential and feeding behavior*

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The relative retention of ^{14}C in the medial hypothalamus as compared to the lateral hypothalamus after intragastric loads of 25 μC of d-glucose-^{14}C was attenuated by pretreatment with 2-deoxy-D-glucose. Using a similar temporal paradigm, it was also found that 2-deoxy-D-glucose prevented the satiating effects of intragastric loads of d-glucose at a point in time when the hypothalamic ^{14}C differential was attenuated. The data indicate that inhibition of feeding by glucose is correlated with greater relative retention of carbon in the medial hypothalamus than the lateral hypothalamus. When this distribution differential is attenuated then satiety is also reduced.

In rats, glucose loads can inhibit feeding independently of osmotic mediation (Booth, 1972; Panksepp, 1971a). Presumably, the inhibition could be mediated via either metabolic or glucoreceptive processes. It has recently been proposed that long-term metabolic control of feeding may be controlled by cells in the medial hypothalamus (Panksepp, 1971b) which have a high capacity to store nutrients (Panksepp, 1972). The presence of higher levels of radioactivity in the medial hypothalamus than in the lateral hypothalamus several hours after ^{14}C labeled d-glucose loads (henceforth designated as the hypothalamic ^{14}C differential) may reflect this integrative process (Panksepp, 1972). The following experiments were designed to assess the behavioral significance of such a measure by determining if covariations exist between feeding behavior and the hypothalamic ^{14}C differential. In an attempt to bring the problem under experimental control, it was reasoned that the hypothalamic ^{14}C differential may reflect the same underlying mechanism which makes the medial hypothalamus susceptible to the cytotoxic effects of gold-thioglucose (GTG). Since GTG induced damage to the medial hypothalamus can be prevented by pretreatment of animals with the glucose antimetabolite 2-deoxy-D-glucose (2-DG) (Likuski, Debons, & Cloutier, 1967), it was hypothesized that both the hypothalamic ^{14}C differential and the normal satiating capacity of glucose would be attenuated by pretreatment with 2-DG.

EXPERIMENT I

In the following study we measured the size of the hypothalamic differential after stomach loads of d-glucose-^{14}C in rats pretreated with saline or 2-DG.

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Method

Ten male and 10 female Sprague-Dawley albino rats were used. The mean body weight of males was 229 g (49-56 days old) and of females 232 g (70-77 days old). Animals were exposed to light on a diurnal schedule (lights on–6:00 a.m.; lights off–6:00 p.m.), and the present experiment was started 4 h into the light cycle. Food and water were available ad lib except as mentioned. Half the animals of each sex were injected intraperitoneally with 750 mg/kg 2-DG (Sigma Chemical Co.) as a 250-mg/ml solution, and the other half were injected with saline carrier. One half hour later all animals were stomach tubed with 25 μC of uniformly labeled d-glucose-^{14}C (New England Nuclear) dissolved in 5 ml of 35% weight/volume unlabeled d-glucose (Sigma Chemical Co.). Six hours later all animals were sacrificed with an overdose of Equithesin. During that interval animals were deprived of food and water. The brains and various tissue samples were promptly removed and frozen on dry ice. Smaller samples were then dissected and weighed to 0.1 mg on a precision torsion balance. Medial and lateral hypothalamic samples were taken from each brain. These brain parts were dissected from a 2-mm wide frontal brain slice which extended from the premammillary area caudally to the caudal border of the optic chiasma rostrally. From this section, medial hypothalamic samples were obtained by making dorsoventral cuts from the fornix columns to the base of the brain and horizontal cuts between the tracts. Lateral hypothalamic samples consisted of bilateral tissue pieces between the fornices medially, cerebral peduncles laterally, and zona incerta dorsally. Optic tracts were excluded from lateral hypothalamic samples and pituitaries, from medial samples. Tissue samples were also obtained from liver, perirenal fat, and abdominal muscle. Tissue samples weighed between 6.2 and 14.5 mg.

Immediately after weighing, tissue samples were placed in counting vials containing 3 ml of tissue solvent and allowed to dissolve for 24 h, whereupon 15 ml of toluene base scintillation cocktail was added to each vial (8 g PPO and 0.2 g POPOP/liter toluene). Samples were counted for 60 min to 1% accuracy. Counts per minute were corrected for background radiation, converted to disintegrations per minute (DPM) by adjusting for channels ratio efficiency scores, and finally expressed as DPM/10 mg wet weight tissue.

Results and Discussion

Since only one tissue exhibited a significant sex

Table 1
DPM/10 mg Tissue 6 H After Intragastric Loads of 25 uC of d-Glucose-^{14}C in Animals Pretreated With 750 mg/kg 2-DG or Saline Carrier

Tissue	Saline (N = 10)		-2-DG (N = 10)	
Muscle	948	±64	650	±65
Liver	1806	±312	4258	±932
Fat	538	±109	407	±50
Medial Hypothalamus	1449	±77	1477	±101
Lateral Hypothalamus	1293	±102	1438	±95
MH/LX ×100%	115.6	±3.4	103.2	±2.6

Note–Values are mean ± SE.

difference, the data have been pooled (Table 1). The one difference reflected the presence of higher levels of radioactivity in the livers of males than females ($t = 3.9$, $df = 18$, $p < .001$).

The 2-DG was found to reduce reliably activity in muscle ($t = 3.08$, $df = 18$, $p < .005$) and to increase levels in the liver ($t = 2.41$, $df = 18$, $p < .025$). Absolute levels if fat, medial hypothalamus, and lateral hypothalamus were not affected. In saline pretreated animals, the typical hypothalamic ^{14}C differential was present, medial hypothalamic samples containing reliably more activity than lateral hypothalamic samples ($t = 4.2$, $df = 9$, $p < .005$), but no reliable differential was apparent in 2-DG treated animals ($t = 1.1$, $df = 9$, $p > .10$). Consequently, the hypothalamic ^{14}C differential was reliably larger in saline than in 2-DG pretreated rats ($t = 2.7$, $df = 18$, $p < .01$).

Clearly, 2-DG can prevent the relatively higher retention of ^{14}C by the medial hypothalamus after d-glucose-^{14}C stomach loads. This was primarily due to increased levels of radioactivity in the lateral hypothalamus rather than to decreased levels in the medial hypothalamus. Although the converse result may have been easier to interpret, the present data still indicate that the same manipulation which decreases retention of GTG in the medial hypothalamus (Likuski et al, 1967) also attenuates the hypothalamic ^{14}C differential, suggesting that both effects reflect a common underlying process. The reason absolute activity in the medial hypothalamus was not decreased may indicate the counteracting effects of two cell populations. The 2-DG may have decreased retention of ^{14}C in specialized storage cells while increasing activity in nonspecialized cells. This possibility is also indicated by the increased activity in lateral, but not medial, hypothalamic samples of 2-DG treated animals.

EXPERIMENT II

If integration of nutrients within the medial hypothalamus controls metabolic inhibition of foot intake, and if 2-DG prevents integration of nutrients within the critical cells of the medial hypothalamus, then postabsorptive satiating effects of glucose should be decreased by pretreatment of animals with 2-DG.

Method

Thirty male Sprague-Dawley albino rats weighing 234-301 g were employed in a within-Ss 2 by 2 factorial design. Animals were deprived of food just prior to pretreatment with intraperitoneal injections of 750 mg/kg 2-DG (Sigma) or saline carrier; ½ h later, half of the animals from each condition were administered intragastric loads of 5 ml of 35% w/v d-glucose (Sigma) and half with 5 ml of saline carrier. Six hours later food (powdered chow) was returned and 1-h food intakes were measured to 0.1 g. Each animal was run through each of the four conditions in counterbalanced manner with 2 days between successive tests. Lighting conditions were as described in Experiment I.

Results and Discussion

Food intakes are summarized in Table 2. Glucose reliably decreased feeding after saline ($t = 3.41$, $df = 29$, $p < .001$) but not after 2-DG. The 2-DG, by itself, reliably increased feeding ($t > 5.38$, $df = 29$, $p < .001$, in both cases).

These data demonstrate that prior treatment of rats with 2-DG can prevent the postabsorptive satiating effects of glucose. Furthermore, it is clear that feeding can be elicited even after a 6-h delay between administration of 750 mg/kg 2-DG and access to food. To our knowledge this is the first attempt to demonstrate 2-DG induced feeding with such temporal parameters.

GENERAL DISCUSSION

These experiments support the idea that integration of nutrients within the hypothalamus may be of importance in the control of feeding behavior (Mayer, 1955; Panksepp, 1972; Panksepp & Nance, 1972). In agreement with our initial hypothesis, pretreatment of rats with 2-DG reduced both the hypothalamic ^{14}C differential and the satiating effect of glucose. This finding lends credence to the idea that the hypothalamic ^{14}C differential may index an event of importance in the metabolic control of feeding behavior.

Although the results do support our initial theoretical formulation, it is not possible to conclusively argue that the observed changes in the hypothalamic ^{14}C differential are in the direct flow of causality in the control of feeding. It should be noted that 2-DG also reduced the absolute levels of ^{14}C in muscle and fat, and the data could be interpreted to indicate that integration of nutrients in those tissues is a critical event in

Table 2
One Hour Food Intake (Grams) After Intragastric Glucose or Saline Injections in Animals Pretreated With 2-DG or Saline

Second Injection	First Injection: Saline		First Injection: 2-DG (750 mg/kg)	
Saline	1.5	±0.3	2.4	±0.3
Glucose (1.75 g)	0.9	±0.2	2.6	±0.3

Note–Values are means ± SE; N = 30 per condition.

the inhibitory control of feeding. Clearly, the present data are too gross for any strong arguments concerning the precise level of action of the observed effects.

Still, regardless of the ambiguities in the possible interpretation of these data, several noteworthy empirical facts were uncovered. First, pretreatment of rats with 2-DG prior to administration of stomach loads of glucose-^{14}C markedly modified the distribution of label within the body while reducing the satiating effect of glucose. These techniques, in combination with more refined analytical tools, may shed considerable light on the locus and nature of metabolic control of feeding behavior.

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Children's paired-associate learning: Response and associative learning as a function of similarity

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The response learning and associative hookup stages of paired-associate learning were studied in 8-year-old children as a function of intralist conceptual similarity. Response learning, as measured by response recall, was facilitated by the presence of similar items, while the associative stage, as measured by a matching test, was somewhat impeded by the use of category instances. These results are similar to those for young adults' learning, and indicate the utility of the stage-analysis model in the study of paired-associate learning by children.

Paired-associate learning has been conceptualized as consisting of two distinguishable stages, namely response learning and associative learning or hookup (e.g., Underwood, Runquist, & Schulz, 1959). The use of a two-stage model has permitted investigators to identify the specific effects of certain variables on the two stages. For example, Underwood, Runquist, and Schulz (1959) found that high intralist similarity facilitated response recall while it had a deleterious effect on associative learning. The facilitation of response recall may be accounted for in terms of reducing S's information load, and the interference in the associative stage is probably related to S's difficulty in differentiating the stimulus items from one another. The present research extends this analysis to children's paired-associate learning.

The use of similar stimuli and responses is common in training children to learn to read, for example. Such popular television programs as *The Electric Company* and *Sesame Street* have employed such similarity manipulations in a modified paired-associate task. However, there has been little systematically collected experimental data on the effect of *interpair* stimulus and response similarity in children's paired-associate learning. The literature on the effects of similarity in children's learning has concerned primarily *intrapair* similarity or *intertask* similarity in transfer, often in an attempt to discover whether or not children use mediators in the same way as adults. Interpair similarity has been less