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REGULATION OF FOOD INTAKE IN THE ABSENCE OF TASTE, SMELL, AND OTHER OROPHARYNGEAL SENSATIONS[1]

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Adult rats and other mammals regulate their daily food intakes with remarkable precision. Attempts to understand the contribution that taste, smell, and other oropharyngeal sensations make to this regulation have been frustrated by the failure of surgical interruptions of the gustatory pathways to produce a complete and permanent loss of taste sensations. Transections of the peripheral pathways (Cranial Nerves VII, IX, and X) in various combinations in the rat have produced only partial and transient deficits (Pfaffmann, 1952) and incomplete degeneration of taste buds (Richter, 1956). Central lesions in the cortical projection areas for the face and tongue (Bagshaw & Pribram, 1953; Benjamin & Pfaffmann, 1955; Bornstein, 1940) and in the thalamic relay nuclei for taste (Ables & Benjamin, 1960; Andersson & Jewell, 1957; Patton, Ruch, & Walker, 1944) in the rat and other species have also failed to produce total ageusia.

The method of direct intragastric self-injection described by Epstein (1960) offers an alternative means for the elimination of oropharyngeal and olfactory sensations during consummatory behavior. Rats with chronic gastric tubes are trained to make an instrumental response that results in the injection of a small volume of fluid through the gastric tube directly into their stomachs. In this way all the oropharyngeal receptors and the olfactory mucosa are bypassed and the animal does not taste or smell the fluids it is ingesting and it does not feel them in its mouth. In fact, it does not make the consummatory response. It merely presses a bar in order to regulate the frequency with which it gives itself an intragastric injection. Rats watered themselves continuously both day and night under these conditions, and they did so with evidence of normal regulation for as long as 7 days.

By replacing the water with a liquid diet, the method has been adapted to the study of feeding behavior. Automatic programing and recording equipment allows the rats to feed themselves night and day according to their natural diurnal cycles. The use of a watertight swivel joint (Epstein & Teitelbaum, 1962) that eliminates the twisting of the flexible tube that connects the animal's gastric tube to the fluid reservoir makes physical restraint unnecessary.

Despite the bypass of the receptors in the mouth, pharynx, and olfactory mucosa by injection of food directly into the stomach and by the elimination of the act of oral ingestion, there are at least two means by which these receptors might still be stimulated during intragastric self-injection. The presence of a tube in the esophagus may predispose to regurgitation of food into the mouth where it may be tasted and smelled; and the absorption of material from the gut and its circulation to the tongue and pharynx may produce some internal taste. If these factors are operating, then intragastric food intake should be depressed by adulteration of the diet with quinine in a concentration sufficiently bitter to reduce oral feeding markedly. If this proves *not* to be the case, that is, if intragastric intake is not at all depressed by such quinine adulteration, then it is reasonably certain that the method precludes detection of the food in the oral and nasal pharynx by regurgitation and internal taste as well as by the ordinary means. The method can then be used with considerable confidence to study long term ad libitum feeding behavior in unrestrained rats ingesting a food that they cannot taste, smell, or feel in the mouth.

Three questions are asked in the work

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reported here. First, do rats feed themselves and maintain their weights normally for prolonged periods of time without sensing the food in the oral or nasal pharynx and without even the act of oral eating? Second, how good is the regulation? Do they respond appropriately and rapidly to abrupt changes in the concentration of the food and in the volume of the individual stomach loads? Third, do they show normal motivation for food ingested this way? That is, do they work harder if required to press the bar more often for each stomach load of constant volume?

METHOD

Subjects

The *S*s were adult female albino rats of the Sherman strain. Four animals were fitted with gastric tubes and were allowed to feed themselves intragastrically. Their average weight was 272 gm. at the beginning of the experiment. Four others ingested food orally in the quinine adulteration experiment. These animals weighed an average of 291 gm.

Apparatus and Techniques

Nasopharyngeal gastric tubes. While the animals were anesthetized with hexobarbital (150 mg/kg IP), they were fitted with chronic gastric tubes that are passed through the nasopharynx and esophagus. The method has been described in detail elsewhere (Epstein, 1960). After insertion into the stomach, the free end of the tube is brought to the outside under the skin of the snout and cranium and projects upward between the animal's ears. This arrangement is shown in Figure 1. Part D is the gastric tube, a 6-in. length of nontoxic, polyethylene tubing (Clay-Adams, New York, PE-50). Part C is a $\frac{1}{2}$-in. length of 22-gauge stainless-steel needle tubing (Superior Tube Co., Norristown, Pa.)

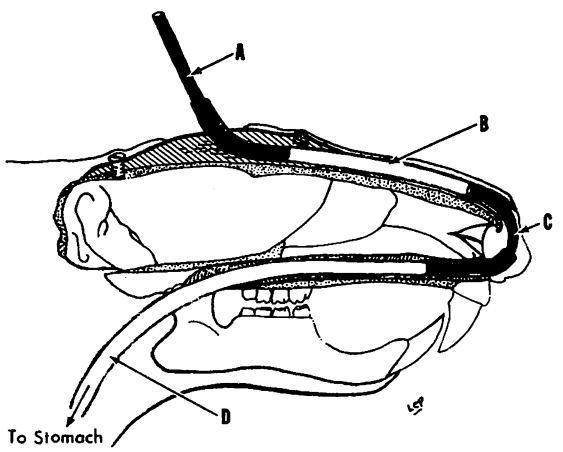

FIG. 1. The course of the nasopharyngeal gastric tube shown in a schematic drawing of a midsagittal section of the rat's head. (See text for details.)

shaped to fit the snout. And Parts B (24-gauge polyvinyl chloride tubing) and A (22-gauge stainless steel) are the inlet to the gastric tube. Polyvinyl chloride tubing (Irvington Division of MMM Co., Irvington, N. J.) is used here for its greater elasticity and durability. The inlet is fixed permanently to the skull with stainless-steel (0–80, $\frac{1}{8}$ in.) screws and methylmethacrylate cement (H. D. Justi & Co., Philadelphia, Pa.).

These tubes have several advantages. They are inserted into the stomach in a minor surgical procedure. They remain in place for many months without infection or respiratory difficulties, and they do not interfere with oral food and water intake.

Watertight swivel joint. The swivel joint (Epstein & Teitelbaum, 1962) is essentially a hollow cylinder, to which the tube from the food reservoir is connected, that rotates freely within a snugly fitting housing fixed firmly to the animal's skull. As the animal circles about its cage, the housing rotates around the cylinder and the tube from the reservoir does not kink. All parts are of Lucite. The cylinder is held within the housing by a flange in its midportion that is engaged by a cap that screws into the top of the housing. The joint is made watertight and is lubricated with ordinary stopcock grease that is applied to all moving surfaces. Completely assembled and greased, the joint weighs 2.5 gm. and is 5 cm. long. The tube from the reservoir is a length of stiff polyethylene tubing (PE-260). More force is required to twist the polyethylene tube than to turn the swivel joint, so only the joint turns with the animal. If the joint is regreased every third or fourth day and if the cap is kept firmly screwed in place, leaks are prevented.

The joint is connected to the gastric tube through a hollow, flexible connector that is forced onto Part A of the inlet to the gastric tube (see Fig. 1) and is included in the cement block held to the skull by the stainless-steel screws. The joint can be removed from the connector when the animal is not injecting itself.

The liquid diet. The liquid diet is an enriched eggnog modified only slightly from that described by Williams and Teitelbaum (1959). The formula for 1,665 ml. is as follows: evaporated milk, 750 ml.; 50% sucrose, 375 ml.; whole eggs, 450 ml. (nine large eggs); Poly-Vi-Sol (multiple vitamin preparation, Mead Johnson, Evansville, Ind.), 1.0 ml.; and Kaopectate (The Upjohn Co., Kalamazoo, Mich.), 90 ml. to control diarrhea. These ingredients are mixed thoroughly in a large container and strained through several layers of cheesecloth. Ten percent formalin in 1.5:100 parts is added to retard spoilage. This diet has approximately 1.57 kcal/ml. It is stored under refrigeration.

The feeding situation and automatic equipment. During the experiment the animals lived in open-topped wooden boxes 8 by 10 by 18 in. with wire-mesh floors. A horizontal slit was cut in the front of the box 2.5 in. above the floor through which the bar could be inserted. The bar was a rectangular piece of thin brass plate (3 in. long, $\frac{1}{2}$ in. wide, and $\frac{1}{16}$ in. thick) soldered at a right angle to the arm of a microswitch. A small round metal food cup ($\frac{3}{4}$ in. diameter, and $\frac{3}{8}$ in. deep) was fixed to one side of the cage just above the floor. When the animal was pressing the bar for oral intake, food was delivered into the food cup through a length of 18-

gauge stainless-steel tubing fixed to the inside wall of the cage. Water was available to the animal at all times from an inverted glass cylinder fitted with a ¼-in.-diameter metal drinking spout (G. H. Wahmann, Co., Baltimore, Md.) that projected into the box to one side and a few inches above the food cup.

By depressing the bar the animal closed the microswitch. This activated a preset subtracting counter (Sodeco, Landis & Gyr, New York) which, after the preset number of responses, started an interval timer (Atcotrol, King of Prussia, Pa.) which in turn activated an automatic pipetting machine (Baltimore Biological Laboratory, Baltimore, Md.). This device is simply a motor-driven 5-cc syringe held in a vertical position. The plunger is fixed eccentrically to the shaft of the motor and is moved through one excursion during each rotation of the shaft. On the down stroke fluid is drawn into the syringe from a reservoir through a one-way valve and is expelled into an outlet tube on the up stroke. The stroke rate and volume can be varied with precision through a wide range. In these experiments the rate was typically set at 1 stroke/5 sec and the volume at 0.5 ml/stroke. The total volume delivered in any single injection was determined by the running time of the interval timer. When the animals were feeding orally, this was usually set at 8 sec. so that approximately 0.7 ml. was delivered into the cup. During intragastric feeding the setting was increased to deliver from 2.0 to 2.5 ml. except when, as described below, the volume of the stomach load was varied. When the interval timer completed its cycle, the pipetting machine was shut off and the timer and the subtracting counter were reset to their starting positions. Fixed ratios (the number of times that the bar had to be depressed to produce a single activation of the interval timer and the pipetting machine) were set by increasing the starting reading of the subtracting counter. Presses emitted during the delivery of a load did not activate the subtracting counter, thus forcing the animal to press the required number of times after each load before obtaining the next load. The total number of bar presses emitted and the number of loads obtained during each day of the experiment were counted automatically and were frequently recorded continuously over time on a Gerbrands recorder set to run at 2 in/hr.

A 250-ml. graduated cylinder served as the reservoir for the liquid diet. The cylinder stood inside a foamed-plastic ice bucket, and the diet was refrigerated by surrounding the cylinder daily with fresh chipped ice. Spoilage in the unrefrigerated portions of the delivery system (the flexible tubes, one-way valve, and syringe) was minimized by washing them in Zepharin solution and water every few days. This spoilage, unfortunately, was not entirely eliminated, and it produced some variation in the sizes of the individual loads on the days when it occurred.

The final arrangement of the apparatus for intragastric self-injection is shown schematically in Figure 2. The ice bucket and diet reservoir are on the left in front of the pipetting machine. The flexible PE-260 tube from the one-way valve is counterweighted over a pulley suspended above the animal's box and is connected to the swivel joint just above the animal's head.

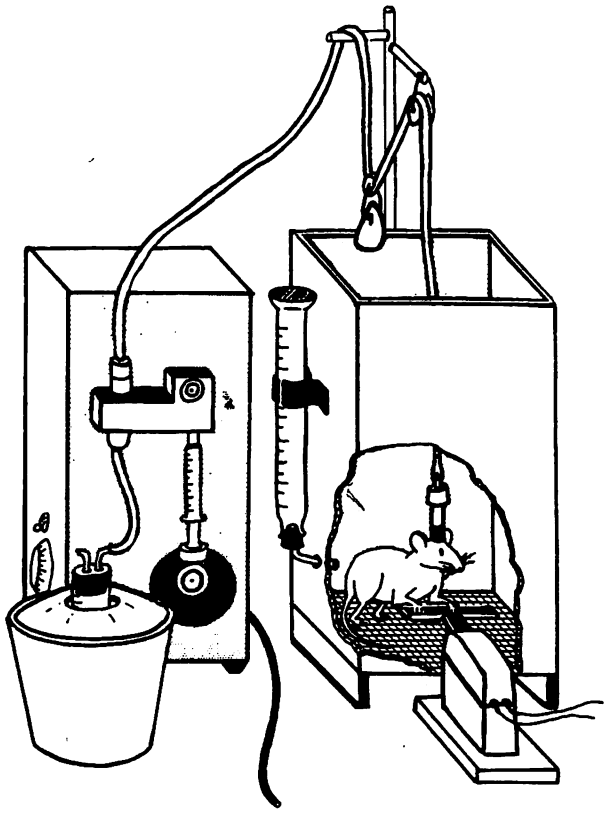

FIG. 2. Schematic drawing of the apparatus for intragastric self-injection by the rat. (The rat presses the bar in order to activate the pipetting machine, center, thus delivering a liquid diet from the reservoir, left, foreground, through the chronic gastric tube directly into its own stomach.)

Procedures and Manipulations

The gastric tube was inserted and the animal allowed several days in its home cage for recovery of normal food and water intake. Under a second anesthesia, the gastric tube inlet and the rubber connector were fixed to the animal's skull. Several days later the animal was placed in the experimental box with no bar present, and small volumes of food were delivered automatically into the food cup on a random schedule until the animal was consistently responding to the noise of the machinery by approaching the cup and ingesting the diet. The bar was then inserted into the box with the predetermined counter set at one (a single press resulted in the delivery of food into the cup), and within a short time (usually overnight) the animal was pressing the bar spontaneously to obtain food for oral ingestion. The number of bar presses required for each delivery of food was then raised gradually to six and left there until the amount of food obtained orally by bar pressing in this manner had remained stable for several days. The swivel joint at the end of the PE-260 tube from the pipetting machine was then inserted into the rubber connector with the animal under light ether anesthesia, and thereafter the food was delivered through the gastric tube directly into the animal's stomach. The animal then fed itself intragastrically night and day

for 5 or more days by pressing six times for stomach loads of approximately 2.5 ml. The diet was then diluted to 50% concentration with tap water for from 1 to 3 days. After several more days of standard conditions (100% diet, FR-5, 2.5 ml. load), the volume of the individual loads was first halved by setting the interval timer at 12 sec. and then doubled by setting it at 50 sec. With all other conditions returned to standard values, the number of bar presses required was then gradually increased to 20 for two animals, and to 36 for a third animal. For three of the animals, the diet was then adulterated with 0.05% quinine hydrochloride (5.0 ml. of a 1.0% stock solution added to 95 ml. of pure diet) for 3 days. Finally, one animal was allowed to feed itself intragastrically for an additional 18 days.

As a control for the quinine adulteration experiment four other animals were given ad libitum oral access to the liquid diet contained in Richter tubes clamped to the side of each cage. They were not required to press a bar to obtain the food. The diet was then diluted with the same concentration of quinine hydrochloride (0.05%) and this mixture was offered to them for 3 consecutive days. Food intake and body weight were measured daily. The experimental animals did not serve as their own controls because prior oral experience with quinine might attenuate its effect in a later test.

Results

Quinine Adulteration

The three animals feeding themselves intragastrically did not decrease their food intake while ingesting a 0.05% quinine hydrochloride adulterated liquid diet for 3 consecutive days. On the other hand, the intake of the four control animals feeding orally was markedly reduced on the first day of exposure to quinine and remained depressed throughout the 3-day test period. The oral *Ss*' intakes in milliliters for a day on pure diet and the 3 succeeding days on adulterated diet were 42, 13, 24, and 36. The corresponding intakes for the intragastric *Ss* were 29, 33, 33, and 30. Daily intake of the quinine-adulterated food by the oral group fell sharply on the first day in all four animals (range, 4–22) and then rose to slightly below normal on the third day of the test (range, 25–41). Averaged across the 3-day period, oral intake of the adulterated food was only 57% of the previous intake of pure liquid diet. This was reflected in an average loss in body weight of 12 gm. suffered by the animals during the same period. The intake of the animals ingesting the adulterated diet by intragastric self-injection was essentially unchanged (range on Day 1, 28–41), and they lost no weight during the quinine test period.

The two groups of animals were not matched for body weight. The average weight of the rats in the oral group was 21 gm. more than that of the intragastric group. This difference accounts in large measure for the greater average intake of pure diet by the oral group.

Intragastric Feeding

The animals feeding themselves by intragastric self-injection regulated their daily food intakes and body weights with remarkable precision for periods of 13 to 44 days (13, 17, 20, and 44 days for individual animals) despite variations in the concentration of the diet, the size of the individual stomach loads, and the number of presses required for a single load. All the animals gained weight during the period of intragastric feeding (in grams: 251 to 257, 263 to 285, 267 to 285, and 298 to 332). Figure 3 shows 3 days of oral feeding and the data of the first 25 days of the intragastric period of the animal studied for the longest time. It includes daily records of body weight, food intake, number of self-loads, and total number of responses (bar presses). The numbers of responses are not exact multiples of the numbers of self-loads because responses emitted during the delivery of the load were counted and are included in the totals.

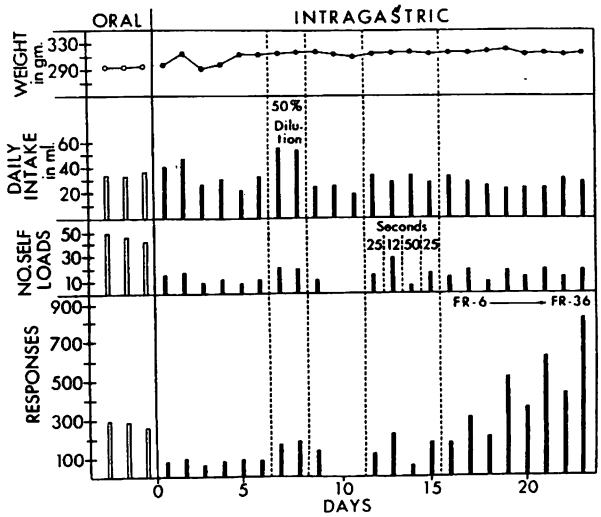

FIG. 3. Body weight, daily food intake, the number of self-loads, and the number of daily responses during 3 days of oral food intake and the first 25 days of intragastric intake. (The number of responses and the number of self-loads are not shown on the tenth and eleventh days because they were spuriously elevated by spoilage and gas formation in the diet.)

Note first that the transition from oral to intragastric ingestion is made with ease, usually with an initial increase in daily food intake. On the fifth day of intragastric feeding, food intake had returned to normal and body weight had increased slightly and had stabilized at slightly above 300 gm. Decreasing the concentration of the diet to 50% by dilution with water resulted in a prompt and sustained increase in intake, number of self-loads, and number of responses. The daily intake and the number of loads were almost exactly doubled, and there was no change in the animal's weight. The adjustment downward on the day after dilution was equally precise. The adjustment of intragastric intake to dilution of the diet was seen in all four animals.

Food intake and body weight are regulated with comparable precision in the face of sudden halving or doubling of the size of the individual stomach loads (reducing the time of activation of the pipetting machine from 25 to 12 sec. and then increasing it to 50 sec.) by appropriate and precise changes in the number of loads taken. While working for a standard load of 25 sec. (2.0–2.5 ml.) on the day before these changes, the animal in Figure 3 obtained 34 ml. of diet by injecting itself 15 times. When the size of the load was halved, the animal obtained 28 ml. in 28 injections, and when the load was doubled, the animal obtained 33 ml. in only 7 injections. The animal kept its daily intake essentially constant by increasing the number of self-injections when the volume of the loads was decreased and by decreasing the number of injections when the volume was increased. Similar adjustments to changes in the volume of the load were made by all four animals.

Finally, total daily responses rose from 180 to 822 as the number of bar presses required to obtain each load was gradually increased from 6 to 36 so that intake and body weight remained well within normal limits. When the usual 6 bar presses were required (Day 15 in Fig. 3) the animal obtained 28 ml. of liquid diet by pressing 180 times for 17 self-loads. One week later, when 36 bar presses were needed for each gastric load, the animal pressed 822 times to obtain 18 self-loads and 29 ml. of diet. The number of bar presses required for each stomach load was increased, in three animals, up to 36 for the animal in Figure 3 and to 20 for two others. All three animals maintained a normal intake despite the increased work load.

Throughout the period of intragastric feeding the animals maintained their normal nocturnal feeding cycles. Small meals (usually 2.5 to 5.0 ml.) spaced several hours apart were taken almost exclusively during the late evening, night, and early morning. Water was drunk, also at night, in the reduced volumes that are typical of animals maintained on the liquid diet employed here. All the animals remained in good health and were active and alert throughout the experiment.

Discussion

The major result of this work is the demonstration that the taste and smell of the food and the feel of it in the mouth are not essential for the normal day-to-day regulation of food intake in the adult rat. The rats studied here fed themselves normal amounts of food and regulated their body weights by injecting a liquid diet directly into their own stomachs on an ad libitum schedule for as long as 44 days. During all of this time the food did not pass through the mouth or pharynx. And at the end of this period, intake was not depressed by quinine adulteration. Taken together, these two facts make it virtually certain that the food did not stimulate any of the receptors in the olfactory mucosa or the oropharynx during the act of ingestion.

The precision of the regulation was remarkable. Intake was nearly doubled when the concentration of the food was reduced by half and was increased or decreased promptly and appropriately when the volume of the stomach load was abruptly doubled or halved. Good regulation was maintained for prolonged periods of time—for as long, in one case as 1½ mo. All four animals gained weight while feeding themselves without oropharyngeal sensations despite the variations in the conditions that occurred throughout the experiment. In addition, the animals showed vigorous motivation for the food when forced to press the bar as many as 36 times for a single stomach load. This supports Miller and Kessen's finding (1952) that intragastric injection of

food is an adequate reinforcement for learned behavior in the rat.

Clearly, the central neural mechanism controlling food intake can operate effectively without receiving sensory information about the taste and smell of the food being ingested or its feel in the mouth and without the proprioceptive feedback from the muscles of mastication and swallowing. Metering by mouth provided by the act of eating is not necessary for the regulation of food intake in the rat. Postingestion factors such as sensations from the gut and chemical or thermal changes in the blood reaching the central nervous system must be sufficient to control the onset of feeding, the size of individual meals, and the total amount of food eaten during a single day and for longer periods of time up to more than a month. Since drinking has previously been shown to be similarly independent of oropharyngeal and olfactory sensations (Epstein, 1960), all the above considerations may be applied to it as well as feeding.

This, of course, does not mean that the sensations from the mouth, olfactory mucosa, and pharynx are of no importance for the management of natural consummatory behavior. They must be crucial for the detection of food in the environment, for the discrimination between the edible and the inedible, and for the rejection of poisons. Specific hungers such as the increased intake of salt that follows adrenalectomy depend upon the animal's capacity to taste salt (Richter, 1956). These sensations make a contribution to satiation as well. Hungry dogs that are allowed to eat but lose the ingested food to the outside through esophageal fistulas do not eat again for as long as 30 minutes (Janowitz & Grossman, 1949). The important conclusion to be drawn from the data reported here is that when detection and discrimination are not required of the animal, the other aspects of feeding and drinking behavior, such as the arousal of hunger and thirst, the satiation of both, and the regulation of intake for prolonged periods of time, can occur normally in the absence of specific sensations from the oropharyngeal and olfactory receptors.

Summary

The regulation of food intake was studied in rats feeding themselves by a method that does not allow them to taste or smell the food or feel it in the oropharynx. By pressing on a bar in order to deliver small volumes of a liquid diet into their own stomachs, the rats regulate the frequency with which they give themselves direct intragastric injections of food. The delivery is made by an automatic pump through chronic gastric tubes that bypass the receptors in the mouth, nose, and pharynx. A watertight swivel joint that eliminates the twisting of the tube that connects the gastric tube to the pump and the use of automatic programing and recording equipment allowed the animals to feed themselves intragastrically both day and night for prolonged periods of time.

The success of the oropharyngeal bypass in eliminating the stimulation of the mouth, nasal mucosa, and pharynx by the ingested food was confirmed by adulterating the diet with quinine hydrochloride. Rats eating a 0.05% quinine-adulterated diet by mouth markedly reduced their oral intake. The rats that fed themselves the same diet intragastrically continued to ingest normal amounts of food.

Despite the absence of taste, smell, and other oropharyngeal sensations, rats regulated their food intake and body weights with remarkable precision for periods of 17 to 44 days. When the diet was diluted to half its concentration with water, the animals doubled their intake. When the volume of the individual stomach loads was halved or doubled, the animals maintained a constant food intake by doubling or halving the number of injections that they gave themselves. The animals showed good motivation for the food by pressing the bar as many as 36 times for a single injection. Normal diurnal cycles were maintained and the animals remained in good health throughout the experiments.

Previous study of water intake in the rat with the same method was recalled, and it was concluded that the taste and smell of the food or water, the feel of them in the mouth, and the proprioceptive feedback from the acts of oral eating and drinking are not essential for the normal function of the central neural

mechanisms regulating food and water intake in the adult rat.

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