Effect of Intragastric Hypertonic Glucose Loads on AC Brain Resistance in Rats.* (28761)

HARRY L. JACOBS (Introduced by C. Ladd Prosser)
Comparative Psychology Laboratory, The University of Illinois, Urbana, Illinois

The rapidity with which systemic glucose can be metabolized and penetrate cell membranes suggests that its osmotic effect is either slight, transient, or non-existent; this is not quite true of exogenous glucose injected into the gastric cavity. In this case the slow intragastric absorption rates and the delay in gastric emptying imposed by hypertonic solutions create conditions where considerable osmotic effects may occur. Several investigators have started from these facts and presented evidence for the critical nature of the osmotic properties of intragastric glucose in controlling food intake. Hypertonic loads of glucose or NaCl inhibit the subsequent intake of glucose solution(1), or of dry stock diet(2,3). The near equivalence of the satiety produced by isosmotic glucose and NaCl loads has been taken to indicate that ingestion of hypertonic glucose satiates the animal *via* a colligative rather than a metabolic route(1,2,3,4). The glucose loaded animal presumably stops eating because further ingestion of dry food or hypertonic glucose would add to the relative water deficit already incurred by the osmotic effects of the loads.

Work in this laboratory has failed to demonstrate the assumed osmotic effects of glucose loads(5,6). The apparent equivalence of glucose and NaCl loads breaks down when animals are allowed a water choice in addition to food. Although an intragastric load of hypertonic NaCl increases water intake while inhibiting food intake, glucose loads show the latter effect only. The apparent thirst-inducing effects of intragastric glucose demonstrated by McCleary(1) have since been shown to be due to deprivation dehydration, and not the glucose load itself(5). The failure of glucose to produce a thirsty animal is incompatible with a simple osmotic explanation of its effects on food intake.

However, Harper and Spivey(7) have shown that forced ingestion of crystalline glucose draws more water into the gastric cavity than ingestion of a high mol wt dextrin. This effect suggests that systemic dehydration may be taking place, but our voluntary intake experiments suggest that glucose loaded animals are not dehydrated and consistently fail to drink water when given a choice(5,6).

What information could the brain be receiving to produce this dissociation between behavioral and physiological events? Recent work by Novin(8) provided the tools for a more direct attack on this question. He has shown that AC brain resistance decreases following hypertonic NaCl loads (*i.v.*), and that the time course of these changes follows the shifts in water balance and drinking behavior demonstrated in classical studies of thirst(9). Although this technique needs validation in biophysical terms, it could still be used to compare changes in brain resistance induced by hypertonic loads of glucose and NaCl and thus help resolve the paradox outlined above.

Methods and materials. The implantation and recording technique was slightly modified from that described by Novin(8). Chronic bipolar platinum-black electrodes, insulated with epoxylite with 3.5 mm tip left bare, were stereotaxically implanted in the brains of 6 female albino rats (250-300 g body wt). Five of the electrode pairs were made of round #28 pt wire; one pair was made of square stainless steel stock (.019 × .019 inch). The first electrode was placed along the midline 1 mm anterior to bregma to a depth of 8 mm. The second entered 4 mm anterior to the first and was inserted at a 15° angle (with respect to the vertical) to a depth of 8 mm. Novin asserts that specific

* This investigation was supported by grants from U.S.P.H.S. and from the Corn Products Inst. of Nutrition.

location is not critical with this technique (8). His early experiments used the aorta as an electrode site. His choice of the brain was simply for the convenience of having the skull as an electrode bearing point to minimize movement artifact.

A Wheatstone bridge and 1000 cycle sine wave source were used in oscilloscopic monitoring of AC resistance. The rats were allowed 2 weeks postoperative recovery time, and then given a series of tests lasting from 30-60 minutes. The source signal was on for 10-15 seconds for each measurement and null detection was made by adjusting capacitance and then AC resistance.

On each test, basal resistance was measured for several minutes prior to intragastric (*s.t.*) or intraperitoneal (*i.p.*) loading of a 1% body wt test liquid; postload resistance was taken at intervals of 30, 60, or 120 seconds. The stability of our resistance measures were evaluated by control tests under sham loading conditions. At least one day's rest was allowed between treatments.

Forty-five experiments were carried out. Treatments consisted of intragastric loads of water, glucose, NaCl, glucose + NaCl mixtures, or sucrose, or intraperitoneal sucrose. Sucrose was added to test the generality of the osmotic argument to all sugars, intraperitoneal sucrose being a known dehydrator equivalent to NaCl, and intragastric sucrose almost equivalent to glucose prior to hydrolysis and absorption.

Results and discussion. In general, basal resistance was quite variable over the 10-week period during which the studies were carried out, averaging 3308 ± 185.8 Ω (± SE), for all observations. Basal resistance tended to decrease over the 10-week period in all animals. Basal resistance was not affected by previous treatments. Since treatment loads did induce drops in resistance which were dependent upon basal level, all measures were transformed to per cent change from basal resistance.

Fig. 1 shows detailed results of 6 of the experiments. The upper series (A) compares the effects of intraperitoneal sucrose with intragastric sucrose. The non-metabolizable in-

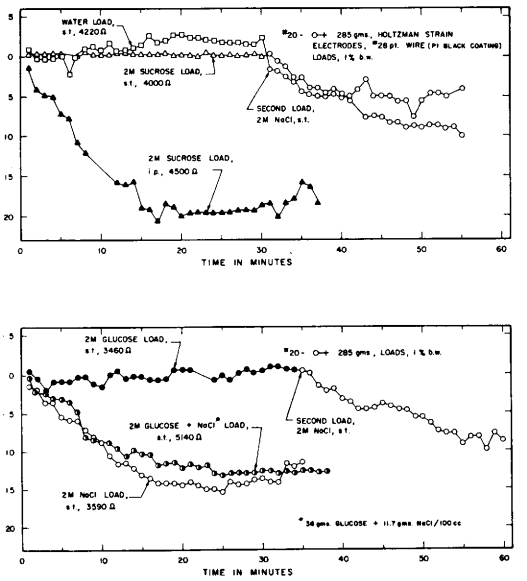

FIG. 1. Effect of various solutions on AC brain resistance. A. (Upper series) Intragastric (s.t.) or intraperitoneal (i.p.) loads of sucrose, water, or NaCl. B. (Lower series) Intragastric loads of glucose, NaCl, or glucose plus NaCl mixtures. In both series, a second load of NaCl was administered when the initial load failed to produce a change in resistance.

traperitoneal sucrose produced a large decrease in resistance. Intragastric sucrose or water loads both failed to change resistance. The addition of an intragastric NaCl load 30 minutes after the initial intragastric water or sucrose load decreased resistance, but the change was much less than that produced by intraperitoneal sucrose administered at the beginning of the experiment.

The lower series (B) carries this analysis a step further by using mixtures to separate intragastric glucose and NaCl. Intragastric NaCl sharply decreased resistance. As in the case of the intragastric sucrose described above, intragastric glucose had no effect on resistance. The glucose-NaCl mixtures produced effects equivalent to the NaCl load, showing that the decrease was independent of glucose. Again, an NaCl load following intragastric glucose decreased resistance much less than did the initial NaCl load.

The full series of comparisons between glucose and NaCl were in agreement with the results presented in Fig. 1. Mean resistance changes 10 minutes after loading were ana-

lyzed for all intragastric loads of these substances in 5 animals. The results were evaluated in terms of the mean percentage change in resistance. Intragastric NaCl loads decreased resistance 6.32 ± .49% (± SE) while 2 M glucose loads slightly increased resistance .83 ± .08% (df=8; t=9.98; P<.001).

Thus, the data are quite consistent in showing that intragastric glucose does not induce changes in brain resistance comparable to that induced by known dehydrators such as intragastric NaCl or intraperitoneal sucrose. These results are in agreement with our previous behavioral work in suggesting that ingested glucose *does not* act as an osmotic stimulus in regulating food or water intake. Also in agreement with our previous behavioral work(5) is the suggestion from the delayed loading experiments that hypertonic intragastric glucose serves to *hydrate* rather than dehydrate the animal.

The discrepancy between our behavioral work(5,6) and the gastric water exchange studies of Harper and Spivey(7) may be resolved by assuming that intragastric glucose may produce osmotic shifts in water balance in the gastric cavity, but that rapid systemic glucose absorption and utilization minimizes the effects so that they are not reflected in comparable shifts in the CNS. This suggests that peripheral dehydration is not a sufficient condition for the appearance of thirst, which is dependent upon the changes reaching the brain. It is only in this sense that these data suggest localization of the thirst mechanism.

Summary. Rats with chronic implanted platinum black electrodes were used to evaluate the effect of various solutions on brain resistance. Intragastric or intraperitoneal loads of water, hypertonic glucose, sucrose, and NaCl, alone or in various combinations were tested. Intraperitoneal sucrose and intragastric NaCl decreased AC resistance, as would be expected from their known osmotic effects in causing shifts of water from the extracellular compartment. Hypertonic glucose loads did not decrease resistance but were equivalent to water loads in their effects because of rapid absorption and cellular utilization. These results are in agreement with previous behavioral studies in showing that ingested hypertonic glucose does not dehydrate the animal and that current notions about the importance of the colligative properties of ingested glucose in controlling food intake are inadequate.

The author would like to acknowledge the technical assistance of Eli Port.

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Received September 3, 1963. P.S.E.B.M., 1963, v114.