apnea (Fig. 1C and Table 1). When 6 percent CO_2 was returned to the respiratory gas mixture before pulmonary blood flow was reestablished, respiratory movements began to return to the normal cyclic pattern. These results indicated that the receptors sensitive to CO_2 were either in the air passageways below the tracheal cannula or in the lungs.

We eliminated the possibility that the receptors were in the extrapulmonary air passageways by cannulating the bronchi at their points of entry into the lungs, thereby eliminating the trachea and extrapulmonary bronchi from the ventilating gas stream. After this, response to CO_2 change remained rapid (Table 1), indicating that the receptors were not in the extrapulmonary air passageways. It thus appears likely that the receptors are in the lungs.

The nerve supply to the CO_2-sensitive receptors was also investigated. Unilateral thoracic vagotomy on either the right or left side at the point of bifurcation of the recurrent nerve only slightly delayed rapid respiratory response time to removal of CO_2 from the ventilating gas (Table 1). Bilateral vagotomy at the same level, however, markedly delayed the response time (Fig. 1D and Table 1).

In these tests, the vagi were sectioned well below the carotid bodies so their nerve supply supposedly remained intact. Elimination of the rapid response to CO_2 removal after bilateral vagotomy indicates that these nerves contain afferent fibers that innervate the CO_2-sensitive receptors in the lungs. That apnea is greatly delayed, but not eliminated, by bilateral vagotomy suggests additional CO_2-sensitive areas in the chicken.

Our results support recent evidence that respiratory amplitude greatly increases after administering 15 percent CO_2 to the separately ventilated, vascularly isolated left lung of the chicken (*9*). Receptors located in the lungs of mammals are sensitive to veratridine and associated alkaloids but have been identified as stretch receptors (*10*). These receptors are not sensitive to changes in carbon dioxide or oxygen tensions in blood (*11*). Attempts to establish the existence of stretch receptors in lungs of the chicken have so far been unsuccessful (*12*).

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3 September 1968; revised 23 October 1968

Separation of Cellular from Extracellular Controls of Drinking in Rats by Frontal Brain Damage

Abstract. *Rats that had undergone removal of the frontal portion of the brain, including the olfactory bulbs, did not drink, or drank less than controls, when subjected to cellular dehydration. These same animals drank normally in response to extracellular volume reduction. Rats from which only the olfactory bulbs had been removed drank normally in both tests. An essential part of the neurological system mediating drinking produced by cellular dehydration, but not by volume reduction, therefore lies within the frontal cortex or immediate subcortical tissue.*

Recent studies of thirst have provided substantial evidence for two components of regulatory drinking, or drinking related directly to body-water deficits. This may be contrasted with nonregulatory drinking which is independent of an animal's hydrational state, for example, prandial drinking, schedule-induced drinking, and some aspects of solution drinking (*1*). One component of regulatory drinking is cellular dehydration. The other is extracellular hypovolemia or a reduction in serum volume (*2*). These components operate independently and when activated simultaneously produce a simple additive effect (*3*).

This independence makes it unlikely that regulatory drinking is subserved by a single neuroanatomical substrate. There may be a neural system for each component. This report shows an anatomical separation of these systems in the rat and it demonstrates that the integrity of the frontal pole area (*4*) is necessary for precise control of drinking induced by cellular dehydration but not for drinking produced by a reduction of serum volume.

Fourteen adult female Sherman albino rats, seven of which had their frontal poles bilaterally ablated by subdural suction (*4*), served as subjects in these experiments. The operated rats were not tested for at least 2 weeks after surgery; at test time their body weights and food and water intakes did not differ from normals. All rats were maintained with free access to Purina lab pellets and distilled water except for the hour before testing (when the pellets were removed in an attempt to insure water balance at the inception of the experiment) and during the test period.

Cellular dehydration was produced by an intraperitoneal injection of 1*M* NaCl (2 percent of body weight). Distilled water was available immediately and the amount drunk was measured at half-hour intervals for the ensuing 6 hours.

The course of drinking in response to cellular dehydration is presented in Fig. 1. All of the normal rats responded

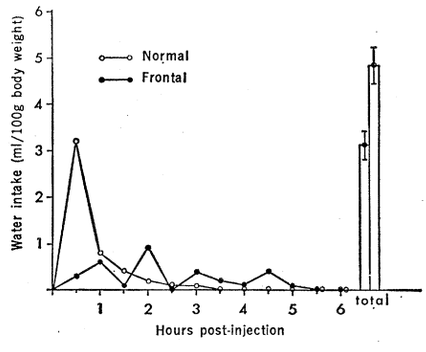

Fig. 1. Mean half-hourly water intake (ml/100 g of body weight) for normal rats and rats with removal of frontal cortex and subcortical tissue. Cumulative intakes (± 1 S.E.) are shown at the right.

quickly and most of their drinking (67 percent) took place within the first 30 minutes. Furthermore, 95 percent of their intake occurred within the first 2 hours, and they did not drink after the third postinjection hour. In contrast, only two of the seven brain-damaged rats responded within the first half hour, and their intake was less than one-third that of normals for that period. The brain-damaged rats drank the most (0.9 percent of body weight) during the 2nd hour and they continued to drink small amounts for more than 5 hours, presumably in response to the osmotic diuresis and consequent reduction in serum volume ultimately following injections of hypertonic saline (*5*). Eventually all seven experimental rats drank, but a comparison of the average total intake makes it clear that they drank significantly less than normal ($t = 3.4$, d.f. 12, $P < .01$).

The suggestion that brain-damaged rats drank in response to the volume reduction resulting from an osmotic diuresis is supported by the findings of a second experiment in which the rats were injected with 2 ml of 2*M* NaCl but were prevented from drinking for 4 hours. Urine was collected hourly and analyzed by flame photometry for Na and K. Neither urine electrolyte concentration (Na plus K) nor volume differed between groups at any time. For example, at 2 hours, lesioned rats excreted 2.4 meq of electrolyte and normal rats 2.5 meq. Furthermore, both groups suffered a net urine loss (total urine excreted minus 2 ml) of 5.8 ml within 2 hours. This diuresis represents a 3 percent reduction in body water which is suprathreshold for extracellular drinking (*2*). The normal renal response to hypertonic saline of the operated rats suggests that their hypodipsia in the initial experiment was not due to a less severe dehydration which would have resulted had they excreted a more concentrated urine. It is suggested that these rats did not drink in response to the intracellular stimulus but drank only when the extracellular compartment was also reduced. This is supported by the fact that most of the experimental rats' drinking occurred after 2 hours, the time that a suprathreshold reduction of body water was achieved.

Additional support for the suggestion that drinking was in response to the volume reduction accompanying the diuresis was marshaled by bilaterally nephrectomizing four different forebrain-damaged rats and three new controls and producing cellular dehydration with a 4-ml intraperitoneal injection of 1*M* NaCl. Nephrectomy prevents urine excretion. Therefore all regulatory drinking following hypertonic saline injections must result from cellular dehydration and none from volume reduction.

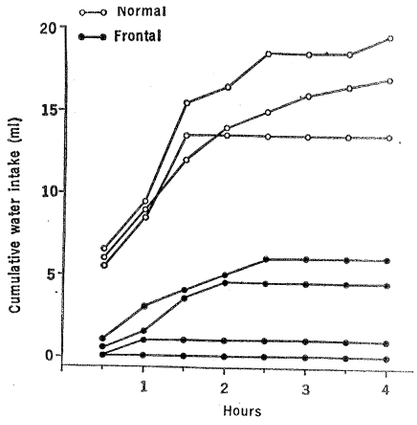

Fig. 2. Cumulative drinking of nephrectomized normal and brain-damaged rats following a 4-ml, 1*M* injection of hypertonic saline.

Figure 2 presents the cumulative drinking of the individual animals. Of the four lesioned rats, one did not drink at all, and another drank 1 ml. The remaining lesioned rats, which probably had insufficient damage to the critical neural area, drank 4.5 and 6 ml respectively, which was considerably less than normals. It is noteworthy that 85 percent of the drinking by these rats took place within the first 1.5 hours. This may be contrasted with the initial experiment where 67 percent of the lesioned rats' drinking occurred after the first 1.5 hours.

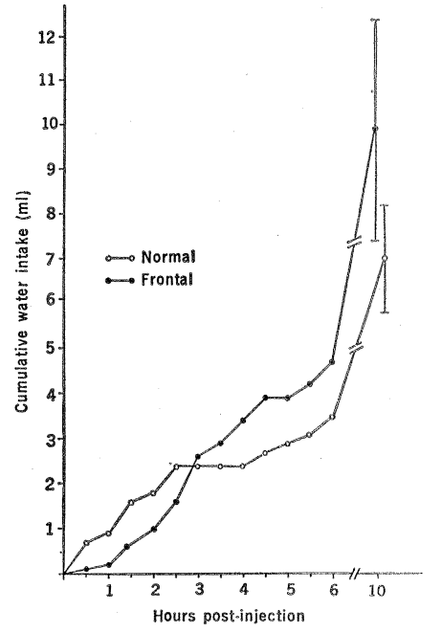

Fig. 3. Cumulative water intake in response to polyethylene glycol for normal and brain-damaged rats. Vertical lines at 10 hours are ± 1 S.E.

In order to ascertain whether the drinking deficit was peculiar to sodium, intracellular dehydration was induced by intraperitoneal sucrose injection (2 percent, by body weight, of 2*M* sucrose). This was done 2 months after the volume reduction described below. The normal rats responded immediately to the sucrose injection and drank an average of 9 ml in the first two postinjection hours. The lesioned rats, however, did not drink at all.

The normal response of the lesioned rats to the blood volume reduction produced by polyethylene glycol is shown in Fig. 3. Hyperoncotic loads draw isosmotic fluids to the injection site, specifically reducing the plasma volume and producing thirst. There is, however, no cellular dehydration (*2*). All rats were injected subcutaneously at the abdominal midline with 5 ml of 20 percent polyethylene glycol (wt/vol). Water was restored immediately and recorded every hour for 6 hours and at 10 hours.

It is clear that brain-damaged rats were not deficient in their response to reduced serum volume. Because the drinking of these rats does not differ statistically from normals either in latency or in total intake, it is therefore concluded that rats with damage to the frontal portion of the brain that do not respond normally to cellular dehydration are unimpaired in volustatic control of drinking.

Because there has been some controversy regarding the contribution of the olfactory bulbs to regulatory drinking (*6*), and the current surgical procedure produces extensive bulbar damage (*4*), the olfactory bulbs were removed without damaging the frontal poles in ten rats that were subjected to cellular dehydration, followed 1 week later by extracellular hypovolemia. Their drinking did not differ from normals either in response to dehydration or hypovolemia. These findings confirm and extend those of La Rue and Le Magnen (*6*), who reported no alteration in drinking following bilateral olfactory bulbectomy.

The forebrain lesion which produced the disassociation of cellular from extracellular drinking was extensive. It completely destroyed the frontal poles

and olfactory bulbs and involved to some extent the following subcortical structures: septal nuclei, anterior commissure, caudate nucleus, globus pallidus, and preoptic area. The latter area is of particular interest because Andersson and Larsson (*7*) have reported that one dog with frontal lobectomy which involved the preoptic area did not drink when injected intravenously with hypertonic saline, but drank normally otherwise. This deficit lasted 3 weeks.

The above findings show that the neurological systems mediating drinking induced by cellular dehydration can be separated from volustatic mechanisms and are consonant with the earlier data of Fitzsimons (*2*) and Stricker (*2*), who demonstrated the physiological separation of the two controls, and with the more recent findings of Corbit (*3*) and Fitzsimons and Oatley (*3*), who found they acted independently of one another. These systems, which are independent structurally as well as functionally, may share a final common path originating in the lateral hypothalamus, because rats that have recovered from lateral hypothalamic lesions do not drink when challenged either with cellular dehydration (*8*) or extracellular hypovolemia (*9*).

The present preparation, in which only the volustatic control is operating, is of special interest because it allows an evaluation of the contribution of the extracellular component to drinking induced by reduction of both cellular and extracellular compartments, as occurs with water deprivation (*10*).

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Sleep after Exercise

Abstract. *After moderate treadmill exercise, marked decreases in operant responding and in latency to onset of behavioral sleep occurs in cats. The sleep produced is characterized by enhancement of synchronized electroencephalographic activity with suppression of the desynchronized phase. The result is consistent with the theory that a function of synchronized sleep is to facilitate recovery from fatigue.*

A causal relation between fatigue and somnolence is strongly suggested by subjective experience. The corollary assumption, that sleep is restorative, is a tenet of common sense. Yet neither of these convictions about sleep has been clearly studied. Evidence showing that either somnolence or hypervigilance can follow exercise has been conflicting (*1–3*); evidence establishing the deleterious effects of sleep deprivation on psychomotor function and the relation between the quality and quantity of deprived sleep with sleep recovered thereafter, is indirect (*4–6*). I now present results of an attempt to clarify the relation of fatigue to subsequent sleep.

Ten adult male cats (3.5 to 5.0 kg) anesthetized with nembutal were operated upon, and electrodes were implanted for long-term electrographic recording. Screw electrodes were placed in the center of each superior orbital ridge for electrooculogram (EOG); screw electrodes were placed in the skull at A10, L5 and at P5, L3 bilaterally for electroencephalogram (EEG); stainless steel wires were fixed deep in the cervical musculature bilaterally for electromyogram (EMG). Fatigue was pro-

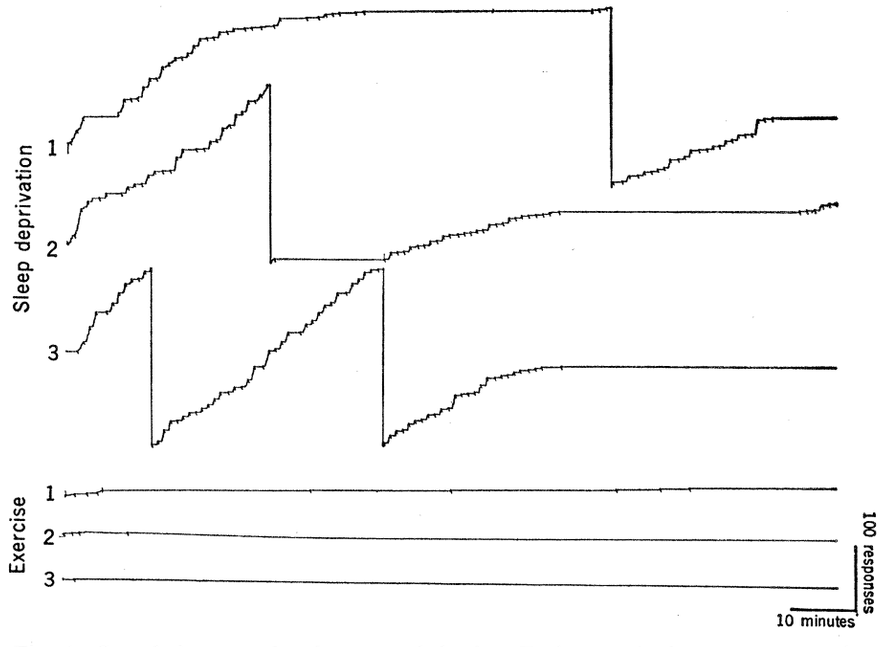

Fig. 1. Cumulative records of operant behavior. Each record plots response against time for the first 2½ hours of the six experimental sessions: a single vertical step is produced by one response, and 275 responses are required to move the pen through its full vertical range, after which it resets to zero; the diagonal hatch marks which are superimposed on the response record indicate reinforcements. Responding during this period was virtually eliminated by exercise.