THE ROLE OF THE RAT IN RESEARCH ON CONTROL OF INGESTION: A COMMENTARY AND REVIEW OF RECENT ADVANCES IN UNDERSTANDING BRAIN CONTROL OF FOOD INTAKE

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Summary

The majority of data concerning the control of food intake in mammals is derived from studies of laboratory rats. Some ingestive controls, identified in rats, seem to operate identically in most farm species. Other controls, which have been identified in nonrodent species, appear to be absent in the rat. Thinking about the neural control of ingestion in agricultural species is based almost entirely on inferences drawn from experiments performed with rats. Recent studies of brain substrates of ingestive control have revealed a prominent role for the caudal hindbrain. Recognition of the caudal hindbrain's participation in the control of ingestion emphasizes the longitudinal integration of brain control of ingestion. Consequently, we must refrain from assuming that the basal forebrain is the unique site for brain control of ingestion. Progress in the investigation of the neural controls of food intake will continue to depend heavily on studies in the rat. Such studies can speed the development of understanding of ingestive controls in farm species by prescribing critical comparative studies. Lack of circumspection prior to initiation and interpretation of such comparative studies can lead, however, to costly misreading of the pattern of ingestive physiology in farm species.

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The Role of the Brain

The rat is certainly not a species of direct economic importance in food, fiber or recreational industries. Nevertheless, this animal has provided the most extensive data base in many areas of animal physiology and especially in the physiology of food and fluid intake. The relatively low cost for acquisition and maintenance of small rodents is undoubtedly responsible, in part, for their popularity in the study of ingestion. In addition, however, most researchers assume that the rat is a "representative" mammal and that controls of appetites in the rat are similar to other species. This assumption, while often correct, appears to be quite wrong in some cases. For example, in the rat the satiety-producing effect of cholecystokinin (CCK) appears to depend on abdominal vagal afferents (Smith et al., 1981); whereas in the sheep (Della-Fera and Baile, 1979; Della-Fera et al., 1981), the predominant effect of this peptide may be in the brain.

There is also current controversy over the mechanisms mediating Na appetite in ruminants vs rats. The research of Epstein and coworkers (Epstein, 1982; Weiss and Epstein, 1983; Zhang et al., 1983) provides compelling evidence that, in the rat, increased appetite for Na is brought about by angiotensin and mineralocorticoid, acting cooperatively on the brain. There is no evidence that the brain monitors Na itself in the interest of controlling salt appetite in the rat. Nevertheless, Weisinger et al. (1982) have recently reported that perfusion of the cerebral ventricles of the sheep with solutions low in Na does elicit increased Na appetite in this species whereas ventricular perfusion with solutions of higher than normal ventricular Na concentration suppresses Na appetite in sheep depleted of Na. Thus Na appetite in the sheep and rat may be controlled by very different mechanisms.
Needless to say, there are other apparent differences between the rat and other species with regard to the control of ingestion.

There are, however, also similarities between the rat and other species. Taste appears to be an important determinant of ingestion in most species of mammals. Increased feeding in response to reduced glucose availability to the brain has been demonstrated not only in the rat, monkey (Smith and Epstein, 1969) and human (Thompson and Campbell, 1977), but also in the rabbit (Houpt and Hance, 1971) and ruminant (Houpt, 1974). The mode of action of CCK in producing satiety in the pig seems similar to its peripheral mode of action in the rat (Houpt, 1983). Finally, it appears that angiotensin elicits increased water intake in most species of vertebrates including rats, fish, ruminants and swine (Fitzsimons, 1978); and it is likely that the role of this hormone in the control of water intake is similar for most species.

In many instances, it is probably not accurate to say that a control exists in one species but not in another. Rather it is likely that certain controls exist in most mammals but are relied upon to different extents in the various species. For example, the satiating effects of oropharyngeal stimulation seem to occur to some extent in species such as the rat and the dog (Grossman, 1960) but do not seem to be of major importance as they are in the horse (Ralston, 1984). It should be mentioned that regardless of the interspecific similarity or dissimilarity of ingestive behavior, essentially all of the experimentally evoked changes in ingestion are simply evidence for the existence of putative controls. It is only assumed that experimental manipulations actually reproduce the activity of control systems exercised under normal physiological and environmental conditions. In this regard, the experiments on suppression of food intake by intraintestinal infusions of hypertonic solutions by Houpt (1984) are most interesting in that he was able to demonstrate that osmotic concentrations comparable to those produced by intraduodenal infusion do occur after spontaneous eating in the pig. His experiments, therefore, are compelling evidence for a role for intestinal osmoreception in the physiological control of food intake in this species.

Ultimately, all controls of ingestive behavior are executed by the brain. Nearly all of our notions about the neuroanatomical substrates of ingestive control come from research with the rat. The relative paucity of direct data on neural substrates of feeding in farm animals is probably due to the difficulty which thick calvaria and relatively variable brain size and shape impose on stereotaxic surgery in these animals. Furthermore, the expense of such experiments and the facilities needed to undertake them place severe constraints on the number of investigators able to study neural substrates of ingestive control in large domestic animals.

It is of interest that our views of neural substrates of ingestive control have been undergoing considerable revision during the last few years, based upon research conducted primarily in rats. One of the most striking changes concerning our views of how the brain controls food intake involves the realization that the caudal brain stem participates in the control of ingestive behavior and in fact subserves some functions previously ascribed to the hypothalamus. Therefore, I would like to focus my comments about central neural circuits controlling ingestion on the dorsal hindbrain.

The caudal hindbrain contains several structures whose participation in ingestive controls seems appropriate. For example, the motor nuclei of the vagus are located within the caudal brainstem and hence the parasympathetic controls of the gastrointestinal tract reside here (Kalia and Sullivan, 1982; Contreras et al., 1982a). The dorso-caudal hindbrain also contains the nucleus of the solitary tract (NST). This nucleus receives most of the primary sensory terminals from the vagus nerve, the glossopharyngeal nerve and the gustatory portions of the facial nerve (Contreras et al., 1982a). In addition, it appears that the NST also receives afferents from the trigeminal nerve (Jacquin et al., 1983). The majority of gustatory afferents to the NST terminate in the anterior portion of this nucleus (Blomquist and Antem, 1965; Burton and Benjamin, 1971), whereas sensory fibers from the vagus dominate the caudal subnuclei (Contreras et al., 1982a). Both rostral and caudal portions of the NST have monosynaptic connections with the insular cortex (Saper, 1982a; Shipley, 1982) and the hypothalamus (Swanson, 1977; Buïjs, 1978; Ricardo and Koh, 1978). Via second order synapses in the parabrachial region, the NST also projects to the amygdala and other portions of the limbic forebrain (Ricardo and Koh, 1978; Saper, 1982b).
Finally, the dorsal hindbrain contains a prominent circumventricular organ, the area postrema (AP). This structure is located dorsomedial to the caudal NST at the obex. The AP, unlike most brain tissue, possesses fenestrated capillaries and is, therefore, devoid of a blood brain barrier (Rohrschneider et al., 1972; Borrison, 1974). Thus, the AP might serve as a receptor area for blood borne signals important to the control of ingestion. The AP has reciprocal neural connections with the caudal NST and possesses direct projections to the parabrachial nuclei (Morest, 1967; Shapiro and Miselis, 1982).

Considering the fact that the caudal hindbrain receives all visceral afferents from the gut, one might expect that termination of ingestion involved hindbrain participation. Nevertheless, until recently most investigators viewed the hypothalamus as the site at which satiety signals were integrated in order to alter food consumption. The research of Grill and his coworkers (Grill and Norgren, 1978), however, clearly indicates that the hindbrain itself can alter consumption in response to naturally occurring satiety cues. These investigators have shown that decerebrate rats (animals who have had the brain transected at the collicular level, thereby disconnecting the forebrain from the hindbrain) can be maintained by placing liquid food in their mouths via a chronically implanted cannula that enters the mouth through the cheek. Although decerebrate rats never eat spontaneously, they do accept food infused into their mouths. Decerebrate animals readily consume sweet solutions but reject bitter solutions by letting them dribble from the mouth and by vigorous mouth wiping. Depriving these animals of food results in greater consumption during the next offering of food. Furthermore, if decerebrate rats are given intragastric preloads, they display a compensatory reduction of consumption when food is subsequently infused into their mouths. These results suggest that the hindbrain contains neural circuits that are sufficient to exert some control of consumption independent of forebrain integration. The nature of the signals integrated by hindbrain circuits has not yet been investigated.

Although it may seem logical that the hindbrain should contain systems involved in terminating or facilitating consumption in response to taste cues or visceral afferents, the hypothalamus has been acknowledged as the seat of all manner of metabolic controls of food intake. The only metabolic control of food intake that can be unequivocally demonstrated, however, is the glucoprivic control. This control is exercised experimentally when cerebral glucose utilization is impaired by reduced availability of glucose from the blood or the administration of an antimetabolic glucose analogue (Smith and Epstein, 1969). Until very recently, the hypothalamus was presumed to contain glucoreceptive neurons that mediated feeding in response to glucoprivation. Indeed, hypothalamic glucoreceptive neurons have been identified electrophysiologically (Ono et al., 1982). Furthermore, several hypothalamic lesions interfere with glucoprivic feeding (Wayner et al., 1971; Bellinger et al., 1978). Despite such suggestive evidence, attempts to elicit feeding by infusing glucose antimetabolites into the hypothalamus have failed (Epstein et al., 1975). Furthermore, there is evidence that lateral hypothalamic lesions do not specifically impair glucoprivic feeding but produce more inclusive motivational and sensorimotor deficits (Stricker et al., 1979). Therefore, there is no direct evidence that the hypothalamus really mediates this control. In fact, recent research in my laboratory has shown that the receptors, which mediate the glucoprivic control, must be located in the hindbrain (Ritter et al., 1981). We showed that microgram quantities of 5-thioglucose (5TG), a potent glucose antimetabolite, elicited feeding when infused directly into the fourth cerebral ventricle, even when passage of the infusate to the forebrain ventricles was prevented by obstructing the mesencephalic aqueduct (figure 1). Infusion of 5TG into lateral ventricles, however, only elicited feeding when the aqueduct remained patent, allowing passage of the infusion to the hindbrain. Subsequently, Flynn and Grill (1983) have found that decerebrate rats increase their consumption of a sugar solution in response to systemic glucoprivation. Our research and that of Flynn and Grill conclusively demonstrates that the glucoprivic control of feeding is not mediated by hypothalamic glucoreceptors. The cerebral receptors that mediate this control are in the hindbrain.

The precise location of the hindbrain glucoreceptors remains unknown. Although Contreas et al. (1982b) have reported that area postrema lesions impair glucoprivic feeding, it is not clear whether this lesion effect is entirely
Feeding in response to infusion of 5-thioglu- 
ose (5TG) into the lateral or fourth ventricle of 
the rat before and after obstruction of the cerebral 
aqueduct. 5-Thioglucose, a potent antimitabolic 
 analogue, was injected in a dose of 90 μg 
in 3 μl. Food intake was measured for 3 h post- 
injection. Values reported represent intake above 
that which occurred following a control infusion 
of artificial cerebrospinal fluid. Intakes following 
control infusions were not different before and after 
aqueduct obstruction (P>.50). Infusion of 5TG into 
the fourth ventricle (N=10) caused more food intake 
than infusion into the lateral ventricle (N=12); 
(P<.05). Obstruction of the cerebral aqueduct abol- 
ished feeding in response to lateral ventricular 5TG 
infusion (P<.01) but did not alter feeding after 
fourth ventricular infusion (P>.10; from Ritter 
et al., 1981).

specific or universally replicable (Hyde and 
Miselis, 1983). Nevertheless, the area postrema 
and the adjacent nucleus of the solitary tract 
remain promising candidates for glucore- 
ceptor localization. One interesting avenue 
that holds promise for localizing the gluco-
ceptors is the use of the cytotoxin, alloxan. 
Intracerebroventricular infusion (ICV) of this 
beta cell toxin has been shown by two research 
groups to impair glucoprivic feeding (Woods 
and McKay, 1978; Ritter et al., 1982). It is 
noteworthy that Ritter and her collaborators 
have demonstrated that the long lasting impair-
ment of glucoprivic feeding following ICV 
alloxan is highly specific. Alloxan treatment 
does not impair other ingestive behaviors and 
does not impair the sympathoadrenal response 
to glucoprivation (Ritter et al., 1982). In 
addition, her research demonstrates that 
alloxan-induced impairment of glucoprivic 
feeding is prevented when alloxan is coinfused 
with D-glucose or amygdalin, two substances 
that protect pancreatic beta cells from damage 
by alloxan (Murnane and Ritter, 1983). This 
finding suggests that the specific mechanism 
of alloxan-induced beta cell toxicity is similar to 
the toxic mechanism exhibited for brain 
glucoreceptors. Ritter et al. (1982) have also 
shown that infusion of alloxan into the fourth 
ventricle is more effective for abolishing glucop- 
rivic feeding than when it is injected into 
the lateral ventricle. Application of this neuro-
cyctotoxin may, therefore, be useful in precisely 
localizing the glucoreceptors for feeding in the 
absence of less specific neural damage.

The rostrolateral nucleus of the solitary 
tract receives the primary gustatory affer-
ents (Blomquist and Antem, 1965; Burton 
and Benjamin, 1971). Therefore, the participa-
tion of the hindbrain as a relay in the taste 
pathways is well studied. On the other hand, 
the extent to which the hindbrain is able to 
alter the behavioral response to taste cues has 
not been examined until recently. It now 
appears that the dorsal hindbrain (AP and the 
adjacent caudal NST) may play a role in chang-
ting taste responsiveness. Although these struc-
tures lie well caudal and medial to the rostro-
lateral portions of the NST, which receive the 
gustatory afferents, there does appear to be 
near communication between the caudal and 
rostrolateral NST (Ricardo and Koh, 1978). 
Therefore, an anatomical substrate that could 
permit the AP and caudal NST to alter taste 
afferent input at the first or second central 
synapses is present.

Recently, we have found that lesions that de-
stroy the AP and damage portions of the imme-
diately adjacent NST (figure 2) alter ingestive 
behavior in several interesting ways. The lesion 
causes immediate loss of body weight, and le-
sioned rats maintain their weight below that of 
controls (Edwards and Ritter, 1981; Hyde and 
Miselis, 1983), although they eventually gain 
weight at the same rate as control rats (Edwards 
and Ritter, 1981). Rats with AP-NST lesions 
display normal 24 h intake of feed and increase 
their intake normally in response to food 
deprivation. Nevertheless, when lesioned rats 
are offered a highly palatable substance, such as 
cookies or a sugar or saccharin solution, we 
have demonstrated that they consume much 
more than do intact rats (Edwards and Ritter, 
1981; see figures 3 and 4). Lesioned rats appear 
as sensitive as intact rats to the suppression of
intake by cholecystokinin or intragastric preloads (Edwards and Ritter, 1981). Severing the subdiaphragmatic vagi does not mimic the effects of the lesion (Edwards and Ritter, 1983). Therefore, the change in ingestion appears to be the consequence of a change of response to orosensory qualities of the food. In this regard, we have found that rats with lesions of the AP and adjacent NST display normal taste preference thresholds for saccharin or sucrose but over-consume both substances at suprathreshold concentration (see figure 5). Quinine rejection functions for lesioned rats are not different from those of intact rats. Thus,
lesions in this area of the caudal hindbrain appear to alter responsiveness to positive tastes. Just how this area may function to change taste responsiveness in intact animals is not yet clear. Research by South in my laboratory indicates, however, that a specific population of neurons that is damaged by the neurotoxin capsaicin may be involved in lesion-induced overconsumption of palatable foods (South and Ritter, 1983). Animals that are given an appropriate dose of capsaicin via the fourth ventricle or directly into the AP over-consume highly palatable foods but do not display any of the other reported sequelae of lesions involving the AP and adjacent NST (Edwards and Ritter, 1981, 1982; Contreras et al., 1982b). Considering the reported neurotoxic specificity of capsaicin (Gamse et al., 1981), it is likely that the action of the AP and NST on taste responsiveness is mediated by peptidergic neurons.

Clearly the caudal hindbrain is an area that does participate in the control of food intake and perhaps in the control of water and Na intake as well (Contreras and Stetson, 1981; Edwards and Ritter, 1982). The extent to which this caudal region of the brain mediates responses previously attributed to more rostral structures is as yet uninvestigated. Furthermore, the role of the hindbrain in the sensation of metabolic need has been proved only for the glucoprivic control (Ritter et al., 1981; Flynn and Grill, 1983). This area may contain receptors that respond to metabolic or endocrine signals other than glucoprivation. The potential participation of hindbrain structures in altering taste responsiveness is also an apparent departure from our view of the forebrain as the seat of emotion and affect. Nevertheless, there are more and more reciprocal connections being demonstrated between the hindbrain and the forebrain (Saper, 1982a, b; Shipley, 1982). We must expect that hindbrain and forebrain damage may interfere with the same neural systems and thereby produce similar, if not identical, behavioral changes. In this regard, I believe that the current trends in research in ingestive controls encourage us to recognize that neural substrates of control probably exist in distributed networks rather than simply in discrete centers (Hyde andMiscelis, 1983). The dissection of these networks and the controls they subserve should be of...
great interest to students of ingestion in farm animals. Nevertheless, small animals, such as the rat, must play an important role in the tremendous volume of neuroanatomy and neurophysiology research necessary to achieve a level of understanding that will permit justifiable studies in larger, more costly species.

**Literature Cited**


