The Biological Nature of Appetite

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ABSTRACT

The brain is responsible for a wide range of appetites or biological drives. The limbic system, and especially the hypothalamus, has been identified as a complex neuroendocrine system that is responsible for physiological regulations and homeostasis, biological drives, appetites, rewards, and hedonic experiences. Two examples are discussed.

1) Hunger and the regulation of food intake are controlled by lateral and medial hypothalamic mechanisms that start and stop eating, but that also exert a neuroendocrine control of metabolism and fat deposition. When these mechanisms fail, there is overeating and obesity, seen in the study of brain-lesioned animals and humans and in genetic predisposition to obesity. The mechanisms involved, however, are extraordinarily complex.

2) Salt appetite represents a simpler neuroendocrine model that has promise of revealing the basic biological principles at work in all appetites. The drive of animals to seek salt licks when they are depleted of NaCl illustrates the significance of this appetite. We now know that depletion of the body of NaCl leads to a synergistic action in the brain of angiotensin and aldosterone, the hormones that operate in salt retention at the kidney. Repeated depletions enhance salt appetite. Blocking angiotensin and aldosterone in the brain eliminates it, even in the face of great need. Selective brain lesions in different parts of the limbic system block the induction of salt appetite by angiotensin and aldosterone separately, and we believe that their synergy may depend on interconnecting pathways between them. Having found critical loci for these neuroendocrine effects, it is possible that identification of the neuronal receptors involved will open the door to a cell and molecular analysis of the mechanism of salt appetite.

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Introduction

Understanding the brain and how it yields behavior is one of the new frontiers of biological science. It is a question of daunting complexity that has puzzled biologists, psychologists, and philosophers for centuries. Recent advances in neurobiology and behavioral science, however, now put us in a position to frame the key questions and seek the answers. The most difficult question, which I will *not* address here, is how the brain produces such complex, cognitive processes as consciousness, reasoning, learning, memory, and perception. Instead, I will concentrate on the simpler question concerning the more stereotyped and hard-wired affective processes such as emotion, appetite, and the biological drives, what ethologists call instincts. To do that, I want to take up two examples. The first is hunger, appetite, the regulation of food intake, and obesity, a problem that concerns many people. Then I will turn to salt appetite and the specific neuroendocrine control of salt ingestion because it is a beautifully simple model system.

The thesis I want to propose is that there is a common mechanism in the brain and a common set of principles governing a wide range of appetites, including hunger and salt appetite, thirst, sexual behavior, maternal behavior, thermoregulatory behavior, fear, aggression, territoriality, homing, and migration among others. The common mechanism is the limbic system at the core of the brain. Its central region, the hypothalamus, monitors and controls the internal environment, including hormones, nutrients, and other blood chemicals, blood temperature, body fluids and osmotic pressure, for example. The limbic system is also responsive to the external environment, the tastes and smells, the touches, the sounds, and sights of the affective world.

The fundamental principle involved is that the appetite which brings the animal into contact with the appropriate part of its environment and the consummatory behavior which results in ingestion are in the service of homeostasis, the maintenance of the constancy of the internal environment. In the process, the brain makes the sensory stimuli involved, such as tastes and smells, highly rewarding and a source of pleasure that can be reported by human beings. So we have a hierarchy of outputs of the limbic system: physiological regulations that maintain homeostasis, drives and appetites that make a behavioral contribution to homeostasis, and rewards and hedonic experience that make up the psychological side of appetite.

The roots of this principle about the function of appetite go back at least to Darwin (1873) who saw the significance of adaptive behaviors like appetites in evolution. A second landmark was the concept of Claude Bernard (1865) of the constancy of the "milieu intérieur" which translated in Walter Cannon's (1932) terms to homeostasis and in E. F. Adolph's (1943) terms to physiological regulations. It was Curt Richter (1942) at Johns Hopkins, however, who saw appetite and the biological drives as self-regulatory behaviors in the service of homeostasis. Today we build on these concepts and ask how the brain produces and regulates appetite and the behaviors that are generated by it.

Appetite and Obesity

Let me first discuss appetite and the regulation of food intake, and the resultant obesity that occurs when the mechanisms go awry. Fifty years ago a focal part of the central circuit in the brain was discovered when Hetherington and Ranson (1942) made small, bilateral, electrolytic lesions in the medial hypothalamus of the limbic system of the rat. Destroying the nerve cells in this tiny region of the brain just above the roof of the mouth has two effects. First, the animal develops a voracious appetite and eats two to four times the normal amount of food, especially if the diet contains highly palatable sugar and fat. Second, we have learned more recently that the lesioned animal secretes excess amounts of insulin which, among other things, drives nutrients preferentially into fat cells, contributing to both the resulting obesity (Fig. 1) and the continuing hyperphagia, for the animal must eat more food to make up for what is being stored away. These effects can be produced experimentally in rhesus monkeys (Fig. 2), and in rare cases, by hypothalamic tumors in humans (Fig. 3). The human case is especially interesting because it illustrates how the experience of ravenous hunger that is difficult to satiate accompanies the hyperphagia.

Further light can be shed on the nature of the mechanisms involved in appetite and obesity by studying strains of rats that are prone to hyperphagia and obesity such as the Zucker rat or the Wistar Kyoto rat shown

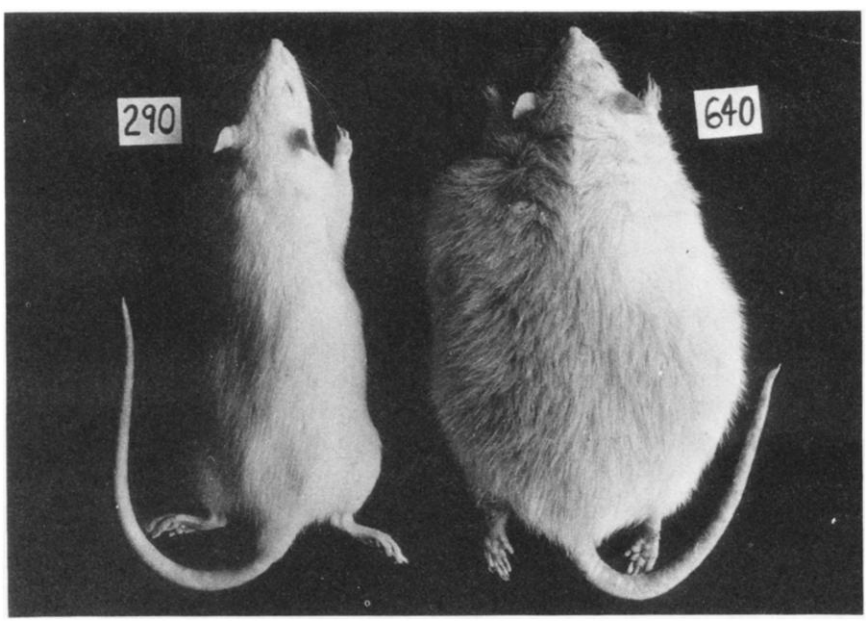

FIGURE 1. The rat on the right was made obese by bilateral medial hypothalamic lesions which caused it to overeat and to store fat preferentially because of the hyperinsulinemia produced by the lesions.

FIGURE 2. **Rhesus monkey made obese by medial hypothalamic lesions.**

here (Fig. 4). In the case of the Zucker rat, the defect seems to be in the high activity levels of the enzyme, lipoprotein lipase, which promotes the preferential storage of lipids in the fat cells (Greenwood et al., 1982). Since pair-feeding these rats the same amount as lean controls still results in a higher percentage of body fat than normal, two things are clear: 1) the animal will deposit fat at the expense of lean body mass and 2) the lipoprotein lipase defect is primary and the hyperphagia is probably secondary. That a genetic factor operates in humans as well is made clear by the twin and adoption studies of my colleague, Dr. A. J. Stunkard (1986 and 1991). The body mass index of obesity in identical twins, including those reared apart from birth, is highly correlated, compared to fraternal twins and siblings. In some ways even more instructive are the correlations seen in the Danish adoption studies where body mass index correlations between children adopted at birth and their biological parents is high and between the children and their adoptive parents, low (Fig. 5).

So we can conclude that appetite and the pleasure of eating play a major role in obesity along with genetic and metabolic predispositions toward the preferential storage of nutrients as fat. Hypothalamic mechanisms within the limbic system function as the core of a neural system

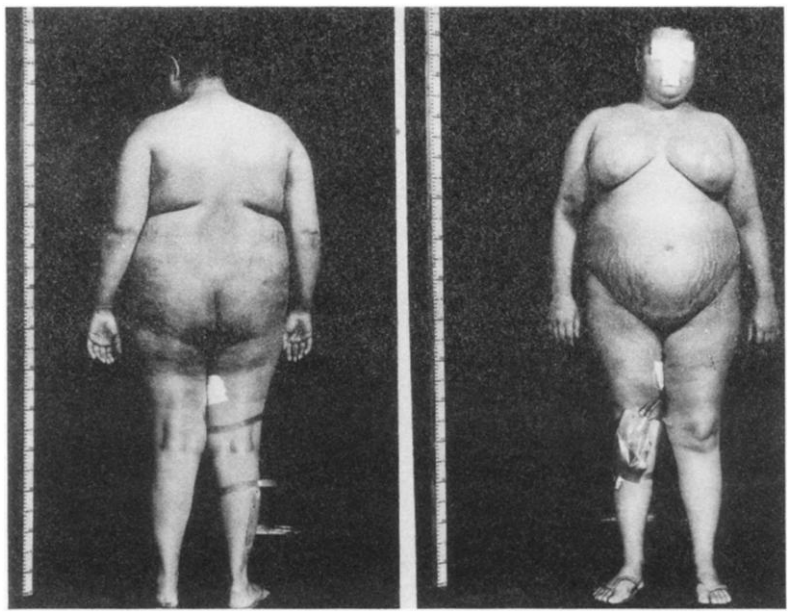

FIGURE 3. **Young woman made obese by a tumor of the medial hypothalamus, causing a very high threshold for satiation and ravenous hunger.**

that operates in the body's energy balance, normally regulating intake of nutrients to meet energy requirements in such a way that the storage of nutrients and adiposity are controlled within narrow limits. Thus, obesity is both a behavioral and metabolic disorder of this neural system with a significant genetic component.

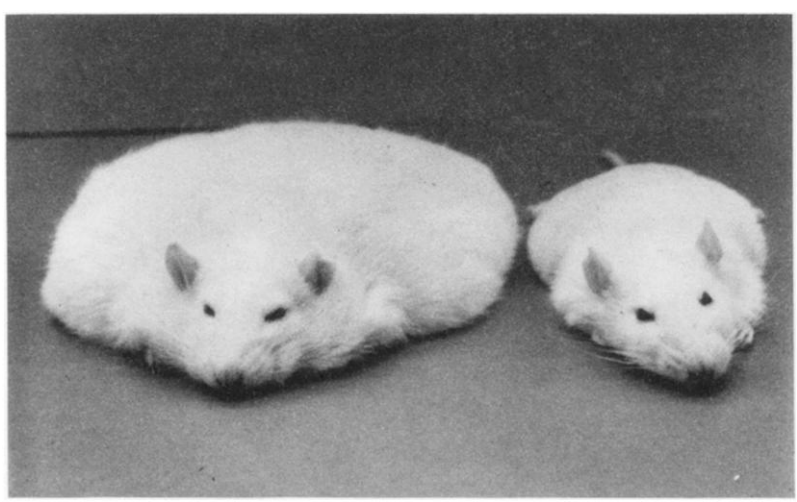

FIGURE 4. **Genetic obesity in the Wistar-Kyoto rat.**

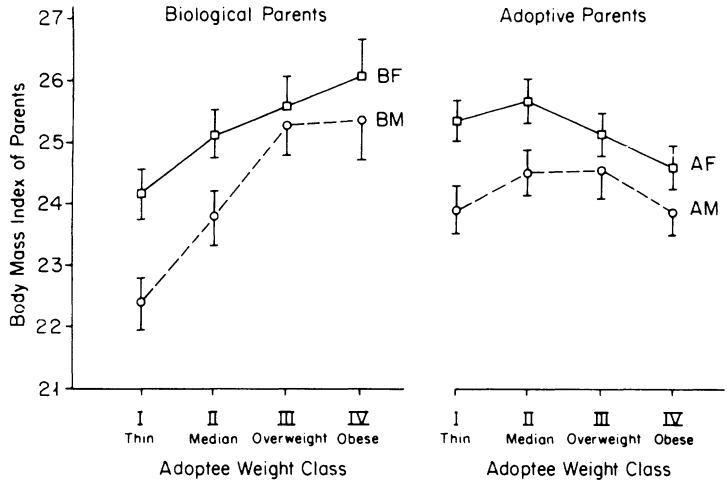

FIGURE 5. Correlation of body mass index of adopted children with their biological parents (left); lack of correlation with their adoptive parents (right).

SALT APPETITE

Because the regulation of food intake is so complex, with many different tastes and smells, nutrients, enzymes and hormones involved, we have turned our attention to the more specific model of salt appetite. In this case, a single taste is involved and, very likely, a specific set of "salt best" fibers in the chorda tympani branch of the VIIth cranial nerve. Also we know specifically that salt depletion is the deficit and we have some idea of which hormones are involved.

The best known example of salt appetite in nature is the salt-lick phenomenon in which animals, living in an inland environment low in salt, develop strong salt hunger and travel great distances to salt licks which are outcroppings of salt and other biologically-active minerals. Typically, foraging for salt is seen in cattle, but it has also been observed in rabbits, birds, and even elephants (Fig. 6) which have been seen entering salt mines and ingesting salt. Salt mines themselves, of course, are great testimony to the human appetite for salt, for salt as Derek Denton (1982) has said is a much-craved crystal and a commodity literally worth its weight in gold at an earlier time in history.

An even more dramatic example of salt appetite is the case of a 3-year-old boy, reported by Wilkins and Richter in 1940. This young boy developed a voracious appetite for salt in his first year of life, licking the salt off crackers and bacon instead of eating them and very quickly discovering the salt shaker, literally eating salt by the spoonful. His life centered around salt and his first word was "salt." Because of his poor appetite and recurrent illnesses, he was hospitalized, and, unfortunately, placed on a strict hospital diet with limited access to salt. Within 7 days he died, and at autopsy, it was discovered that he had adrenal gland tumors which had destroyed his ability to make aldosterone, a hormone that con-

FIGURE 6. **Female elephants and their young, satisfying their salt appetite in salt mine.**

serves salt at the kidney. Thus he was losing salt in his urine relentlessly. He had obviously been keeping himself alive by ingesting salt as fast as he was losing it. Investigated in the laboratory rat by C. P. Richter (1936), the adrenalectomy preparation became a model for the study of salt hunger, for it allowed him to remove the hormone, aldosterone, by the adrenalectomy and to replace it by injection or implantation. As expected, adrenalectomy produced salt appetite and replacement of aldosterone at low doses eliminated it. Curiously, at high doses aldosterone produced the appetite in the adrenalectomized rat and in the normal rat as well. We'll come back to that.

Many years later, Bryant, Epstein, Fitzsimons, and Fluharty (1980) showed that infusing angiotensin into the ventricles of the rat induced the animals to drink large quantities of hypertonic salt solutions. Their finding is quite interesting, for angiotensin appears to be a molecule critical in body fluid homeostasis and a major factor in the regulation of blood volume and blood pressure as well. As Figure 7 shows, it has a number of related actions. It is synthesized in the brain as well as the periphery. In addition to promoting salt intake, it promotes the release of aldosterone, and together, angiotensin and aldosterone act as the hormones of salt retention at the kidney. Angiotensin, as already mentioned, is also a potent dipsogen and stimulates the secretion of vasopressin from the pituitary, promoting water retention at the kidney. Finally, angiotensin is a constrictor of blood vessels. So, here we have a molecule critical in body fluid homeostasis and blood pressure. In the face of loss of water and electrolyte as in hemorrhage or diarrhea, it promotes salt and water retention at the kidney, salt and water appetite in the brain, and constriction of the vascular system to maintain blood pressure.

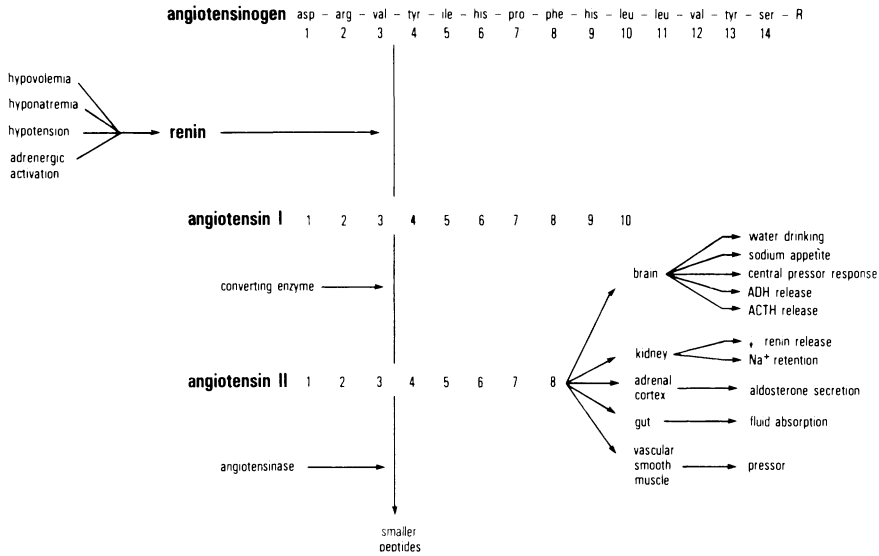

FIGURE 7. The many functions of angiotensin in the brain, at the kidney, the adrenal cortex, the gut, and the blood vessels, contributing to the regulation of body fluid balance and blood pressure control.

The specific guiding hypothesis about salt appetite, put forward by my colleague, Alan Epstein (1982), is that sodium depletion activates both angiotensin and aldosterone to work in synergy in the brain to produce salt appetite and the ingestion of salt. Evidence for this synergy became clear when it was found that subthreshold doses of the two hormones produced very robust salt intake and caused rats to run rapidly in a runway to reach small tastes of a salt solution, something they simply won't do unless in the state of salt deficit (Zhang, Stellar, and Epstein, 1984). In these experiments, angiotensin was injected into the ventricle of the brain and aldosterone or its mimic, DOCA, which cross the blood-brain barrier, were injected systemically. The animals were not depleted of salt, but ran for it because the hormones in the brain elicited salt appetite.

The easiest way to produce robust salt appetite for experimental purposes is by depletion. The protocol is to treat rats with a diuretic and natriuretic, furosemide, put them on low sodium diet, clean their cages of ambient sodium, and let them drink water ad libitum. The first time they are depleted of sodium chloride this way, they drink large amounts of 3% NaCl solution in a two-hour intake test. However, if they are depleted again one week later, they drink almost twice as much as Figure 8 shows (Sakai et al., 1987). This is not a matter of learning to drink salt solutions, for even if the rats are not allowed the experience of drinking 3% NaCl after the first depletion, but make up their depletion by eating their sodium-rich regular diet, they still show enhanced salt-solution drinking. What is more, they don't even have to be depleted, for admin-

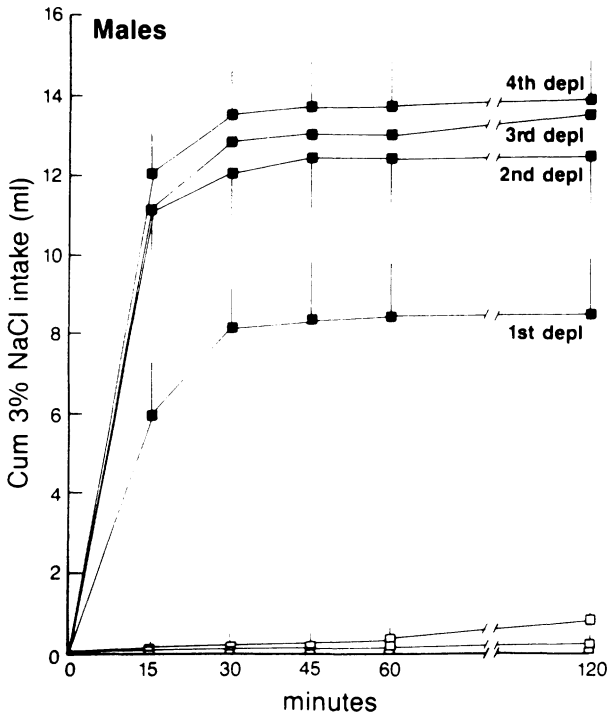

FIGURE 8. **The enhancement of depletion-induced salt appetite in the rat by prior episodes of salt depletion.**

istering angiotensin and aldosterone a week before the depletion test results in enhanced intake. By some means, as yet unknown, the effect of depletion is permanently to alter the adult brain hormonally and predispose it to higher levels of salt appetite and ingestion. This conclusion has implications for human health, for episodes of diarrhea, hemorrhage, excessive sweating may all lead to severe sodium depletion and thus excessive salt appetite.

What makes the enhancement of salt intake even more significant is that it is not limited to depletion-induced intake. When the daily intake of 3% NaCl and water are monitored during the weeks between depletions when the rats are salt replete (Fig. 8), it is clear that a history of sodium depletion leads to enhanced salt intake when the animals have no need for extra salt (Sakai et al., 1989). So the change in the brain due to salt depletions can lead to a chronic salt appetite and excessive salt intake.

Another striking finding to emerge from these experiments is that female rats drink over twice as much 3% NaCl solution as male rats (see Fig. 9). This sexual dimorphism has been shown to be the result of neonatal testosterone blunting the mechanism for salt intake, for neonatal castration makes male rats drink like females, and neonatal testosterone

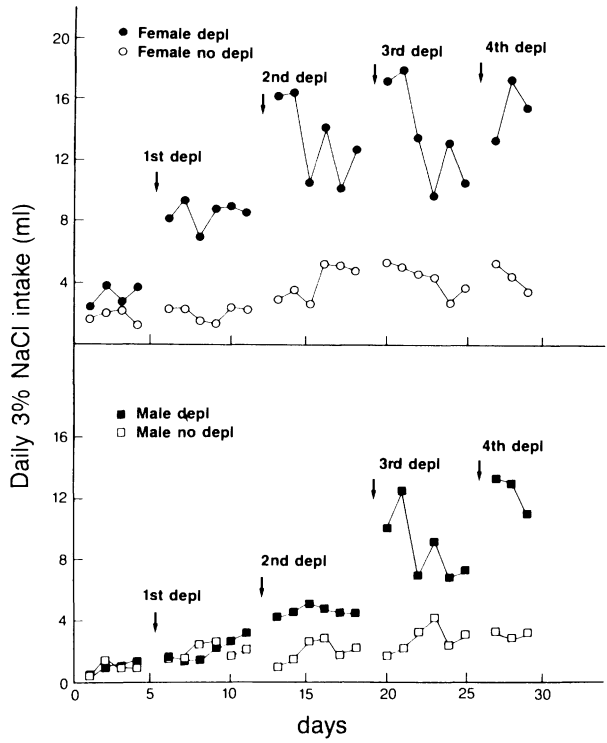

FIGURE 9. **The enhancement of need-free salt appetite, due to prior depletions. Note that female rats ingest almost twice as much salt as males.**

reduces female salt intake to male levels. From an evolutionary point of view, it makes sense for the female to be more responsive to salt depletions, for it must ingest extra NaCl to supply sodium to its offspring during both pregnancy and lactation.

Finally, definitive evidence for the synergy of angiotensin and aldosterone comes from experiments in which the actions of these hormones are blocked in the brain (Sakai, Nicolaidis, and Epstein, 1986). In the case of angiotensin, captopril that blocks the enzyme that converts angiotensin I to its active form angiotensin II is injected into the ventricles. For aldosterone, a receptor-blocker, RU-28318, is administered intraventricularly. Remarkably, when either angiotensin or aldosterone alone are blocked, intake of 3% NaCl is reduced to about half. When both are blocked together, the appetite for salt, induced by depletion, is virtually eliminated (Fig. 10). The power of this approach is further illustrated by blocking angiotensin in the adrenalectomized rat which, of course, has no aldosterone. These animals stop drinking salt when, in fact, their lives depend on it (Sakai and Epstein, 1990).

Thus, we may conclude that angiotensin and aldosterone, hormones of salt conservation, are also hormones of salt appetite, acting in the brain. As Figure 11 shows, peripheral angiotensin stimulates aldosterone

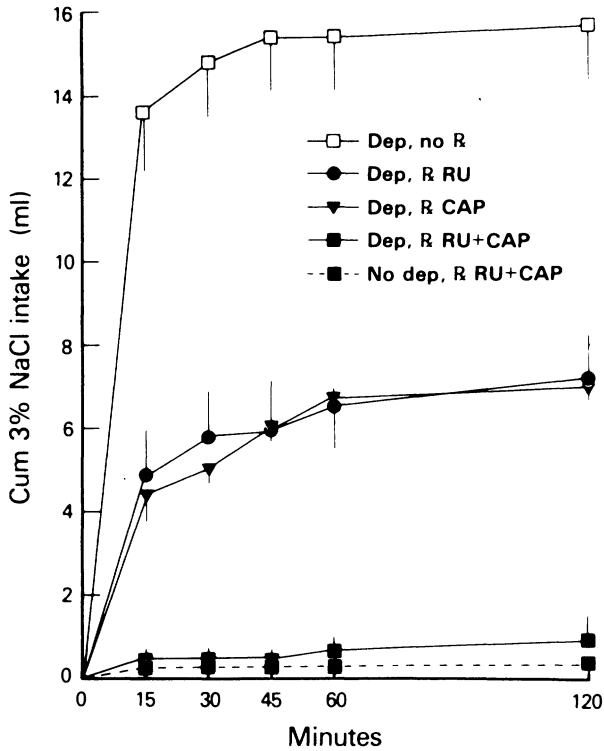

FIGURE 10. **The elimination of salt appetite in the face of severe depletion by blocking angiotensin and aldosterone actions in the brain.**

release from the adrenal cortex, and aldosterone works to retain salt at the kidney. At the same time, aldosterone crosses the blood-brain barrier, and together with angiotensin of cerebral origin, creates the brain state that leads to salt appetite.

Given these results, the next question is where in the brain do the hormones of salt appetite act. Both angiotensin and aldosterone have receptors in many parts of the brain, subserving many different functions. Using electrolytic lesions to eliminate areas of concentrated receptors in the brain regions thought to be important, Epstein and Schulkin and their students have identified candidate structures in the limbic system that might subserve the angiotensin-aldosterone synergy. Lesions of the medial amygdala knock out aldosterone receptors and eliminate salt appetite due to aldosterone or DOCA administration, but not depletion- or angiotensin-induced salt intake (Nitabach, Schulkin, and Epstein, 1989). Lesions in the anterior wall of the third ventricle, the so-called AV3V region, do essentially the opposite (DeLuca et al., 1991). So the question becomes how do the respective influences of aldosterone and angiotensin in these two regions add up to produce the synergy. The answer, we think lies in part at least, in the pathways connecting the amygdala and the AV3V region (Fig. 12), and these are now being ex-

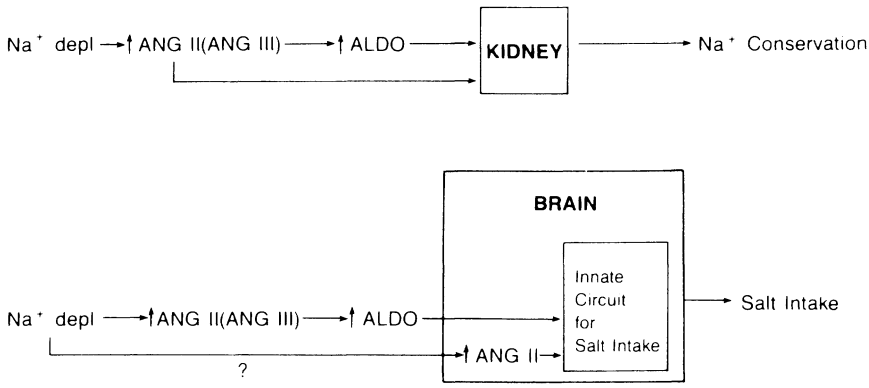

FIGURE 11. **Epstein's proposed synergy of angiotensin II and aldosterone in producing salt conservation at the kidney and a brain state leading to salt appetite and salt intake.**

plored by making knife cuts that interrupt the pathways and should eliminate the synergy.

Given the identification of loci of the two kinds of receptors in the brain, it now becomes possible to use molecular and genetic probes to identify their origin and their sensitivity to various treatments known

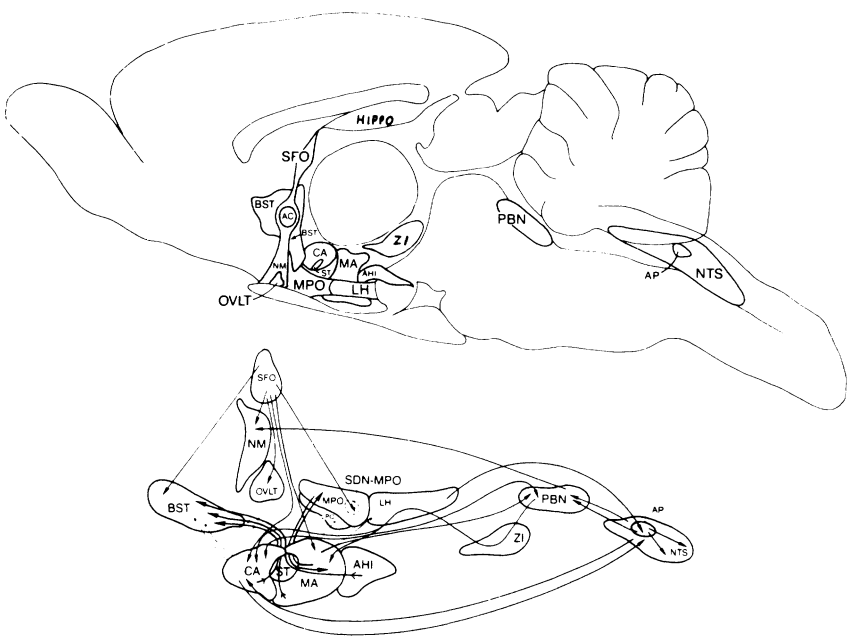

FIGURE 12. **Brain circuits proposed by Schulkin, connecting the medial amygdala (MA) where aldosterone is believed to act and the AV3V area (SFO, BST, NM, and OVLT) where angiotensin of cerebral origin is believed to act in producing the synergy that leads to salt appetite.**

to increase or decrease the appetite for sodium chloride. At the same time that we try to reduce the nature of salt appetite to those fundamental biological levels of analysis, however, we also have to make the synthesis that lets us understand the complex limbic brain circuits that yield reward and hedonic experience.

Conclusions

1) Appetite is controlled by the state of the internal environment through neural circuits of the limbic system of the brain.

2) The neural circuits are activated by the same hormones that play a role in homeostasis and by sensory stimuli such as taste and smell as well.

3) The output of this neural circuit not only produces the appetite and ingestion, normally matched to the state of bodily need, but it also produces the substrate for reward and the experience of pleasure that can be reported by humans.

4) Alterations of these neural circuits, their receptors, or the internal environment controlling them by genetics, disease, tumor, or the hormonal environment of the brain can lead to disorders of appetite such as hyperphagia and obesity or excessive salt ingestion.

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