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BRAIN MECHANISMS AND HEDONIC PROCESSES

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Abstract. This paper attempts to take a broad view of investigations of brain mechanisms of motivated and emotional behavior in animals and humans. It examines the thesis that the same basic brain mechanisms are involved in physiological regulations, in various motivated behaviors and emotions, and in the hedonic experiences that can be reported by humans. It further suggests that reward and the reinforcement of learning depend on the same brain systems. Finally, it speculates on the possibility that these same brain systems play an important role in the selection of what is learned and in the consolidation, storage, and retrieval of memory. To present this conceptualization, selected experiments in thermoregulatory behavior, electrical self-stimulation of the brain, evoked approach and withdrawal behaviors, and the role of neuropeptides in thirst and hunger are reviewed. In addition, experiments will be discussed in which memory is blocked by puromycin, but in which puromycin-induced amnesia can be prevented by the administration of certain peptides such as vasopressin and some of its fragments. Speculation about the common underlying mechanism and its biological significance in the adaptation of the organism is discussed as are some of the experiments suggested by this line of thinking.

Since I have been away from the laboratory for six years as a University administrator, I cannot tell you about the results of any new experiments I have done. However, the separation from active research may have given me some perspective, so I would like to take advantage

of the opportunity and review some investigations I have been involved in the past in the light of some of the remarkable advances that have been made in our field while I was away. Particularly, I want to review experiments of some of my closest associates, former students and colleagues at the University of Pennsylvania. My hope is that I can develop new insights of how the nervous system can work in behavior, especially in those aspects having to do with hedonic processes, including motivated behavior, reward and the reinforcement of learning, and also human subjective experience of pleasure and pain, those positive and negative hedonic experiences that we can rate and report.

This will be quite a speculative approach, for I will want to make the thesis that the same broad system within the brain is involved in all kinds of motivated behavior, reinforcement, and hedonic experience. Not only that, I will want to speculate further that the same mechanism plays a major role in the selection of which adaptive changes in the organism's behavior are learned and remembered, possibly leading us to one of the keys to the biological basis of memory. To make the speculation worthwhile, I will want, of course, to have it lead to laboratory experiments, and I will tell you about some I am involved in and have contemplated in the four months that I have been back in the laboratory.

I would like to begin by discussing some experiments in thermoregulatory behavior, for that allows us to tie together animal and human work as well as physiological regulation, motivation, reinforcement, and hedonic experience. Then I would like to go on to experiments in brain stimulation and reinforcement that might tell us something about learning and memory; then experiments on hunger and thirst that involve the peptides; and finally in a speculative leap, how study of the peptides may provide new insights into the biological basis of learning and memory.

Let me turn to thermoregulatory behavior first. Heating and cooling the brain, particularly the anterior hypothalamus, evoke heat loss and heat production physiological responses such as panting and shivering in the dog and saliva-spreading and piloerection in the rat. Using the rat, John Corbit (4) was able to show that heating or cooling the hypothalamus also leads to behavioral thermoregulation. His experimental set-up, shown in Fig. 1, allowed him to investigate the behavioral effects, not only of heating and cooling the hypothalamus, but also of heating and cooling the skin, and the interaction between the two as well.

In a nutshell, Corbit was able to show three things. First, that rats worked very hard pressing a lever for a 15-s change in temperature

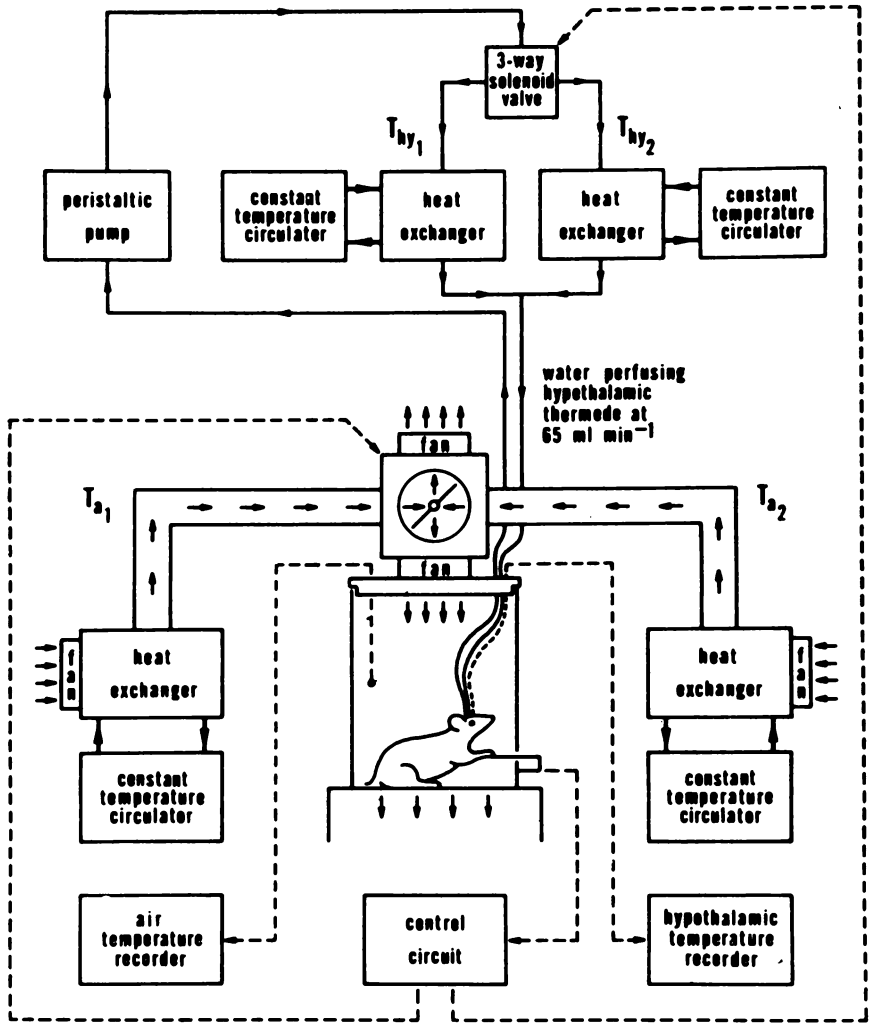

Fig. 1. Diagram of experiment in which a rat can perform instrumental conditioned responses to control the temperature of air in its chamber (bottom) or the temperature of water flowing in and out of thermodes implanted in its brain. From Corbit (4).

of the air or of the water flowing in and out of the small steel thermodes implanted in the anterior hypothalamus. The more extreme the ambient or the brain temperature, the more rapid the instrumental responding, as illustrated in Fig. 2 which shows the rate of responding for a 15-s flow of cool water through the thermode as a function of increasing brain temperature. Second, there is an interaction between

the central and peripheral mechanisms, so that warming the skin will motivate the animal to cool its brain, for example. As Fig. 3 shows, the higher the skin temperature, the more the rat will work to cool a given brain temperature. Third, the animal can tell where its problem is, for when its brain is warmed, it prefers to cool its brain rather than cool

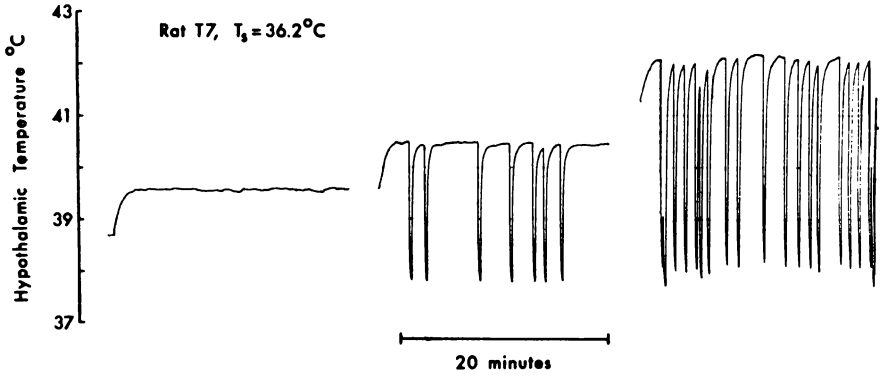

Fig. 2. Rate of instrumental responding for a 15 s lowering of brain temperature as a function of increasing basal brain temperature. From Corbit (4).

its skin if given the choice of two different instrumental responses, pulling a chain to cool the air or pressing a lever to cool its brain (5). Thus, we have clear evidence for motivated thermoregulatory behavior in which thermal change functions as an excellent reinforcement for learning instrumental responses and discriminations as well.

To investigate the hedonic experience associated with such instrumental learning under thermal reinforcement, one of my graduate stu-

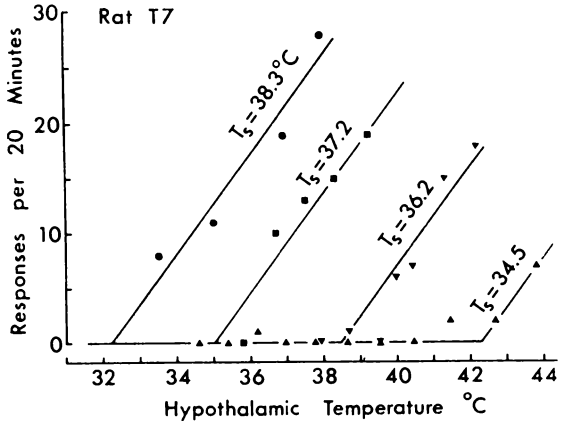

Fig. 3. Rate of instrumental responding to cool brain temperature as a function of different skin temperatures. From Corbit (4).

dents, Ray Hawkins (12), did a parallel study of human subjects. In his experiments, volunteer subjects sat in a constant-temperature tub up to their necks in warm or cool water. After a shorter or longer period of time, we had the subject stand on a stool just out of the tub water and turn on a shower which was at tub temperature. The subject was then allowed to operate a dial that controlled the shower temperature over a wide range, with the instruction to find the most pleasant shower temperature. Rectal temperature was recorded throughout the experiment.

As shown in Fig. 4, if the subject was allowed to sit in the tub long enough to raise (High T_i) or lower (Low T_i) body temperature by half

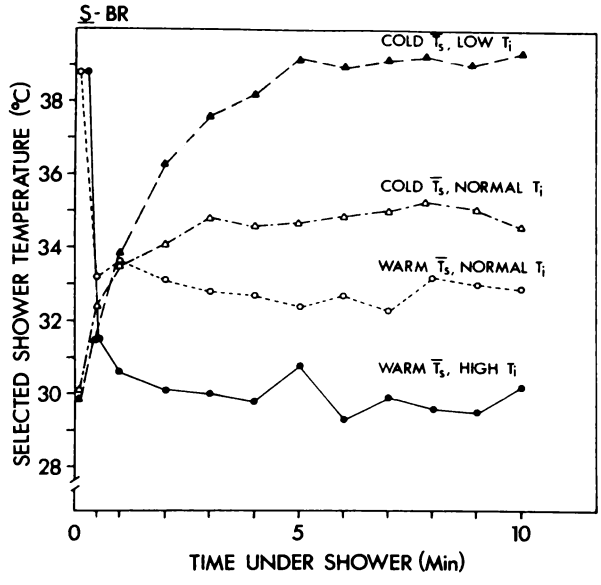

Fig. 4. Shower temperature selected as most pleasant by a human subject as a function of skin temperature (T_S) and internal or core temperature (T_i). From Hawkins (12).

a degree, he took a shower of extreme temperature. Thus, if rectal temperature was raised, he took a very cold shower for as long as ten minutes. Furthermore, he reported the experience as highly pleasurable. This is the familiar sauna effect, followed by the proverbial hedonistic roll in the snow. The same was true if body temperature was lowered, for a long, hot shower was described as just as pleasurable. If, however, the subjects took the shower before rectal temperature changed (Normal T_i), then shower temperature was less extreme and the hedonic experience modest.

The same result was found, following the procedure of Cabanac (3) in which the subjects rated the hedonic value of different hand temperatures. If body temperature was lowered, then dipping the hand into a water bucket of high temperature was rated most pleasant and vice versa as Fig. 5 shows. Thus, both humans and animals vigorously per-

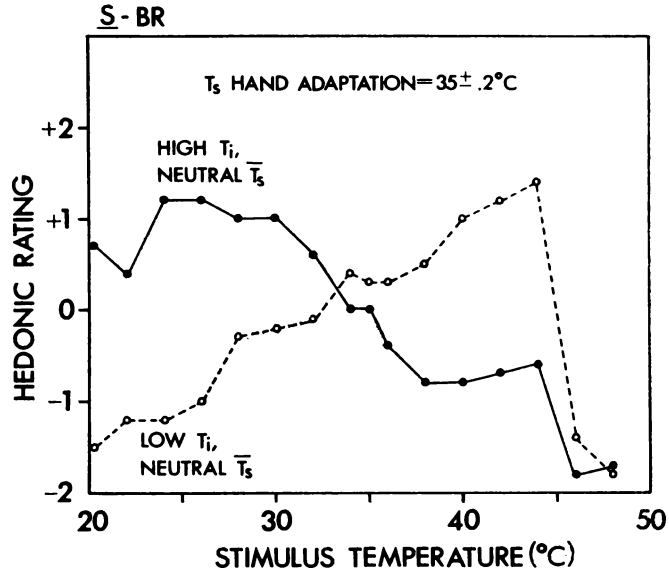

Fig. 5. Hedonic ratings of hand baths (stimulus temperature) as a function of internal temperature (T_i) controlled by a whole body bath. From Hawkins (12).

form instrumental responses which are motivated by changes in core temperature, and therefore, brain temperature. In humans, these motivated behaviors are accompanied by clearly reportable and strong subjective feelings or experiences of thermal comfort and discomfort, pleasantness and unpleasantness. Presumably the same brain mechanism generates the motivated behavior and the hedonic experience. This mechanism also contributes to the physiological regulation of body temperature and it participates, moreover, in the reinforcement of instrumental learning. In fact, using thermal changes in the brain as a reinforcement is another way of conducting the intracranial self-stimulation experiment, using temperature rather than electrical stimulation.

Let us turn now to electrical self-stimulation of the brain, for this remarkable discovery (15) led Olds to postulate "pleasure centers" within the brain. As he investigated the brain mechanisms underlying this phenomenon, he showed that there were extensive positive and negative

systems, involving the same lateral and medial structures running through the hypothalamus and limbic system that seemed to be involved in motivated behavior.

Gallistel's experimental analysis of intracranial electrical self-stimulation into a drive component and a reinforcement component is most instructive to our thinking. In his investigations, rather than have the rat press a lever repeatedly to deliver intracranial stimulation as Olds had done, Gallistel had the rat learn the instrumental response of running down a runway to a goal-box where it could press a lever for lateral hypothalamic stimulation (11). Before the animal was placed in the runway, it was given a priming stimulation through the same electrode. Running speed was used as the measure of performance, and it was found that the more intense the priming stimulation, the faster the running. Also, the more intense the rewarding stimulation in the goal box, the faster the running. But there was a big difference. The effects of priming begin to decay in about 90 s although they sometimes last up to 10 min; the animal would run very slowly, if at all, after such a delay, even though the priming stimulation might be very intense. The effects of stimulation in the goal box, on the other hand, seemed to last a long time, at least overnight and perhaps longer, for if the animal received intense stimulation at the end of one day, it began its running at high speeds when tested the next day, for example. So it seemed as though the animal remembered what the goal-box stimulation was like from one day to the next.

Further experiments by Gallistel and his co-workers (10) have shown that there are two different populations of neurons involved in priming and reinforcement as judged by their characteristic refractory periods. One population may be described as the rapidly decaying, longrefractory-period (1.0 ms) neurons involved in priming and drive. The other population is made up of long-lasting, short-refractory-period (0.6 ms) neurons involved in reward and reinforcement and perhaps also in memory.

Using these same electrodes that produce self-stimulation, my son, Jim Stellar (19, 20), working in Gallistel's laboratory was able to make animals approach various objects and stimuli and react much more positively to them. For example, with lateral hypothalamic stimulation, rats reacted to a weak sugar solution in the mouth as though it were a strong, positive solution, and they pursued it very avidly when it was withdrawn. Lateral hypothalamic stimulation even made them react positively to a noxious odor they would normally avoid or reject and it served to attenuate or eliminate their startle response to loud noises and their escape or avoidance of electric foot shock. On the other hand,

medial hypothalamic stimulation often made rats withdraw from objects they normally approached and made them unresponsive until positive stimulation was made very strong. Thus, with medial hypothalamic stimulation, it was necessary to increase the concentration of a sugar solution by a factor of ten to get the animals to respond positively to it. So it appears that electrical stimulation of the medial and lateral hypothalamic areas can bias the hedonic balance of the brain in either the positive or the negative direction, toward approach or withdrawal, acceptance or rejection.

Two other recent advances by colleagues at the University of Pennsylvania add fuel to my thinking. In one set of investigations in Alan Epstein's laboratory (7), it is becoming ever so much clearer that the octapeptide, angiotensin II, is playing an important role in motivated behavior, in both thirst and salt appetite. If angiotensin II is injected into the subfornical organ of the circumventricular system (Fig. 6) (16) then minute amounts of angiotensin, measured in femtomoles, will elicit

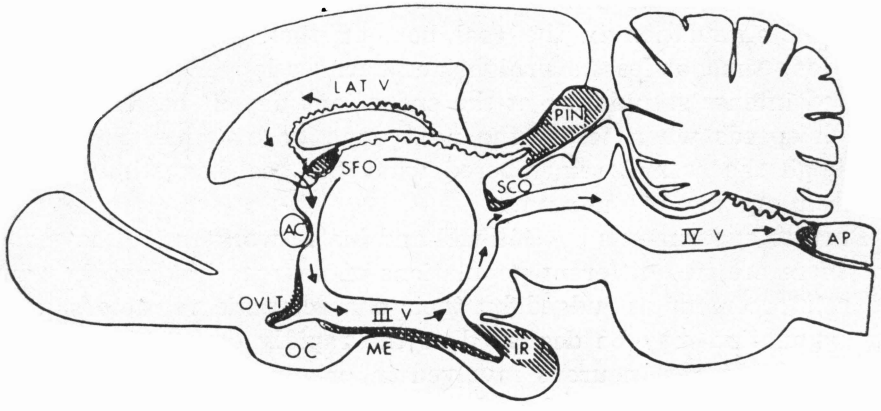

Fig. 6. Diagram of the seven circumventricular organs of the rat's brain. SFO, subfornical organ; OVLT, organum vasculosum of the lamina terminalis; ME, median eminence; IR, infundibular recess and neurohypophysis; SCO, subcommissureal organ; PIN, pineal; AP, area postrema. From Phillips (16).

drinking (Fig. 7). Angiotensin is a potent dipsogen, indeed. If it is continuously and slowly infused into the ventricles, then the rats will drink as much as their body weight in water per day. That would be the equivalent of a man drinking 50–60 l a day! In addition, rats which drink virtually no 3% sodium chloride solution, drink enormous quantities of this solution, as high as 150 ml in 24 h (2). What is more, in some animals, the salt appetite may persist for months after the infusion

even though water drinking returns to normal when the angiotensis is stopped.

Angiotensin, as you know, is synthesized in two steps in the body by the kidney hormone, renin, and by a converting enzyme in the lung. It now appears that the same renin-angiotensin synthesic sequence occurs entirely within the brain, so angiotensin is a brain peptide. A si-

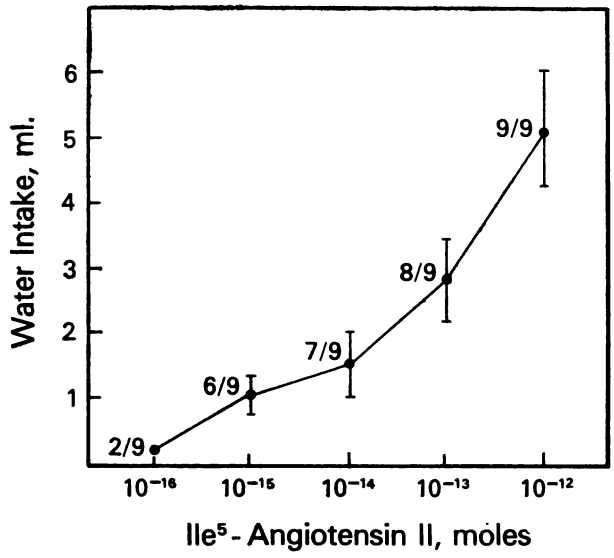

Fig. 7. Drinking elicited by injection of different concentrations of angiotensin II into the subfornical organ. Threshold is between 10^{-16} and 10^{-15} mol. From Epstein (7).

milar story is unfolding about the peptide, cholecystokinin (CCK) which is secreted by the intestine in response to food in the stomach. Experiments by Smith and his colleagues (17) in which CCK is injected systemically show that it is a satiety factor, for it causes a cessation of eating in rats and all the behavioral signs of satiation. It turns out that CCK is also made in the brain, and recent work by Yalow and her co-workers (21) has shown that the brains of genetically obese mice have about one-third the amount of CCK as their lean controls. At the University of Pennsylvania, Della-Fera and Baile are showing that injection of minute quantities of CCK-octapeptide into the ventricles of sheep causes marked reduction in food intake (6). Finally, preliminary findings by Kissileff and co-workers (14) at St. Luke's Hospital in New York indicate that human subjects, administered CCK systemically, report satiety and reduce their food intake.

Quite clearly, the brain peptides can play an important role in hunger and thirst and perhaps other kinds of motivated behavior as well.

Given what we are learning about the endorphins, peptides also seem to be important in pain perception and mood as well. It is not surprising, therefore, that de Wied and others (22, 23) have asked about the role of peptides in learning and memory, particularly vasopressin, some of its fragments, and related peptides. This possibility appeared particularly attractive to my colleague, Louis Flexner (8), when he discovered that vasopressin, given 12 h before or 24 h after a learning experience could protect mice against the amnesia induced by the antibiotic, puromycin. Some of the fractions of vasopressin, oxytocin, and other peptides were even more potent in their protection against puromycin-amnesia.

Although we originally thought that puromycin blocked memory because it inhibited protein synthesis in the brain when we first published our results on puromycin in 1963 (9), it is now clear that puromycin also has other effects, including inducing prolonged hippocampal seizures and altering catecholamine levels, especially reducing noradrenalin levels. This finding is interesting because the peptides which protect the animal against puromycin-amnesia also have effects on catecholamine levels although as far as I know, there is no evidence that one action counteracts the other.

How to understand the role of the catecholamines in learning and memory is not yet evident although Stein (18) has shown the role of noradrenalin in intracranial reinforcement. Speculation by Kety (13) suggests that the catecholamines play an important role in the brain as well as in the periphery in the adaptions of the organism. He sees the catecholamines functioning in biologically significant situations of a positive (eating, drinking, sex) or negative (pain avoidance) sort to select and reinforce synapses that may be active during the learning process. He believes that the catecholamine fibers are particularly well-suited to this function, for (i) they operate in circumstances of high motivation, reward, and reinforcement; (ii) they find their way to the cortical surfaces of the cerebrum, cerebellum, and hippocampus and wind around the large dendrites there or run along the surface in close proximity to the cerebrospinal fluid (CSF) surrounding the brain; and (iii) 95% of them end without synapses, secreting their neurotransmitter substances around the dendrites and possibly in the CSF. This conception suggests a neural network system, involving widespread structures in the brain, in which the engram is laid down in many synapses that are repeatedly active during biologically and emotionally significant events. If this is so, we must find a way to ask how it is that puromycin can block this mechanism and how the peptides can protect against the block and facilitate learning and memory.

At the present time, Dr. Flexner, Jim Sprague, and several other colleagues and I are engaged in examining the effects of depleting dopamine in the suprasylvian gyrus of split-chiasm cats by topically bathing it with 6-hydroxy-dopamine. Berlucchi, Sprague and their colleagues (1) have shown that lesion of the suprasylvian gyrus results in slow learning by the eye on that side, but good transfer of training to the other eye. In contrast, the contralateral eye learns rapidly, but there is little or no transfer to the eye ipsilateral to the lesion. Our question is whether we can find similar defects with local catecholamine depletion and whether vasopressin or other peptides will attenuate those deficits. In addition, we hope to investigate the role of the brain peptides in other learning situations in the mouse, rat, and cat, using visual discriminations, delayed alternation, and possibly delayed-matching-to-sample.

All of this is still quite speculative, but I would like to conclude now and make three points about the central mechanisms of motivation that are involved in instrumental conditioning.

1. I believe that the same brain mechanism is involved in physiological regulations and in a wide variety of motivated behavior which contribute to the regulation of the internal environment (hunger, thirst, thermal behaviors), as well as other motivated behaviors which are not concerned with physiological regulation or the survival of the individual (sexual, maternal, aggressive behaviors).

2. The same brain mechanism participates in the generation of hedonic experience in man, in approach and withdrawal behavior, and reinforcement in animals and man.

3. Are these same mechanisms also involved directly in the acquisition, consolidation, storage, and retrieval of memories? Are the peptides one of the important keys to our future experimental elucidation of the biology of memory? We shall see.

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