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Peptides and Protocritic Processes

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INTRODUCTION

The organizers approached this conference with a unique proposal. They have asked some of us who are ignorant of the wealth of research findings on the role of brain peptides in behavior to comment on that wealth. I seized this opportunity to learn and find out just what is known. After reviewing the chapters I experienced an unusual postprandial satisfaction. Part of this satisfaction is due to a decision reached in the reading. Two modes of review were open to me: One, to have tried to organize the material to be reviewed on its own merits, or two, to try to integrate the peptide results into the frame of theory already developed on the basis of other data, especially those from my own laboratory. I chose the integrative approach as being the richer, but realized the difficulties of exposition which then had to be faced. For it must be made clear that I did not approach the peptide data with any view toward forcing them to the frame. Rather, the data evoked their own clear organization, an organization which paralleled that obtained from the other research data.

The frame of the theory regards what I have called protocritic processes. The term is derived from Head (35) who, on the basis of experiments in which he severed his own peripheral nerves and studied his sensations as regeneration occurred, discerned two modes of feeling: an epicritic and a protopathic. Epicritic sensations carried local sign i.e., they allowed the stimulus to be referred to a point in space-time. By contrast, protopathic feelings, which occurred while the nerves were regenerating and before they had reestablished their normal spectrum of fiber-sizes, globally reflected the intensive dimension of the stimulus.

In Head's experiments these protopathic sensations were clearly linked to pathology-the cut nerves. Subsequent research, however, showed that two classes of nerve fibers, distinguishable by their fiber size were responsible for the two types of sensation: a large diameter system with a fast conduction rate mediates epicritic processes, while a set of small fibers is responsible for protopathic sensations (26).

Much of this research has dealt with pain and discomfort. Recently, the relationship between epicritic and protopathic processes has been viewed as somewhat more complex than just two parallel systems. Melzak and Wall (53) have proposed that epicritic processes act as a "gate" on the protopathic-i.e., when there is sufficient organization of input in space-time, protopathic sensations are eliminated.

Once the gate theory had been forwarded a further complication became apparent. In tracing the ventral spinothalamic tract-the severing of which abolished pain (85)-cephalad, only about one-third of the fibers reached the ventrobasal thalamus and parietal cortex. The other two-thirds of the fibers disappeared along the way, many of them ending in core brainstem structures such as the periaqueductal gray and medial thalamus (44).

These anatomical data were supplemented by the results of psychosurgical procedures undertaken to assuage pain and distress. Parietal cortex resections helped little while frontal leukotomies did (93) and frontal cortex received its input from the medial thalamus (67, 69). What then, might be the relationship at the thalamic level between epicritic and protopathic processes? Could a ventrobasal-parietal (or, as Mountcastle suggested some years ago [54], a closely related posterior thalamic-posterior parietal system) act as a gate on the more medially placed corebrain-frontal system? And perhaps vice versa?

PAIN AND TEMPERATURE

These questions would remain unanswered as long as we knew little about the corebrain-frontal mechanism involved in the protopathic process. However, to study pain in the animal experimental laboratory is difficult. Threshold studies can of course be done readily, but the organism's behavioral response to aversive stimulation is primarily one of escape and avoidance-and these measures entail such other factors as level of activity, memory, conflict, etc., which, as the reports presented at this conference make clear, pose problems of analysis for the experimenter.

In order to circumvent some of these problems, I searched for another sensory modality closely related to pain, that would not bring with it these disadvantages.

In the spinal cord, the pathways for pain and temperature appear to be inseparable. The temperature sense thus suggested itself as an obvious candidate for exploration. Further, just as in the case of pain, parietal lobe excisions had failed to influence temperature discrimination in a host of studies (17). Perhaps the cortical involvement in temperature, as in pain, is frontal rather than parietal.

An experiment was performed in which temperature discrimination was disrupted by electrical stimulation of the posterior orbital surface of the frontal lobe, the amygdala and the stria terminalis (11). Parietal lobe stimulations had no such effect. These results suggest that a neural system based on the pain and temperature modalities may remain separate not only in the spinal cord but through the brainstem and into the forebrain. The orbital locus of the rostral terminus of the system is not far removed from the site of the temperature regulating mechanism in the anterior hypothalamus; it should not be altogether surprising to find the regulatory and discriminative functions adjacent to one another.

In the brainstem and diencephalon the sites from which pain (aversive response) can be obtained are adjacent and often intermingled with those from which positive reinforcement due to electrical self-stimulation is elicited. Further, as is now well-known, electrical stimulation of many of these sites with low frequency (10 to 20 hz) currents produce analgesia (47, 48) and when such stimulations are performed in man sensations of cooling accompany the analgesia (78).

These data suggest the hypothesis of a neural system-or set of systems-based on the pain and temperature senses-that deal with the hedonic dimension (distress-comfort). As noted earlier, the term protocritic (rather than protopathic since discrimination not pathology is critical) distinguishes these systems from the epicritic which deal with organism-environment relationships in space-time (58, 63).

THE AMYGDALA

The central locus of the effect of electrical stimulation on temperature discrimination is the amygdala. (The other two effective sites, the oribital cortex and stria terminalis are respectively the source of a heavy input to the amygdala and serve its output.) The amygdala, classically classified as a basal ganglion and

more recently as a part of the limbic forebrain, has over the past 30 years received considerable attention from the neuroscientific community (see 19). In addition to influencing temperature regulation (82) and discrimination (11), the amygdala has been implicated in a complex of behaviors initially brought together under a rubic "the four F's"-Feeding, Fighting, Fleeing, and Sex (57, 59, 66, 75). The involvement of amygdala function was then further extended to encompass a variety of problem solving behaviors related to reinforcement (83), stimulus equivalence (4, 36, 37, 84), delayed alternation (71), the orienting reaction (1, 3), and classical conditioning (2).

These apparently disparate behaviors can be shown by careful analysis to be influenced by a common mechanism (28, 60, 64, 72). It is worth summarizing the highlight of this analysis because identifying a common mechanism operating on apparently disparate behaviors is a recurring problem in neuroscience as it is in genetics (where it involves identifying genotype from phenotypical behaviors).

With regard to feeding, the amygdala has been shown to be a modulator of the satiety mechanism centered in the ventromedial region of the hypothalamus. First, it was noted that the increased feeding of amygdalectomized subjects was due to their failure to *stop* eating as readily as their controls (24). Then, a very precise relationship was established between the amounts of carbachol injected and amount of feeding (or drinking) once they had been initiated (33, 80).

This modulation of a *stop* mechanism was also shown responsible for changes in fighting behavior. Fall in a dominance hierarchy after amygdalectomy was, when it occurred, related to the amount of aggressive interaction between the dominant and submissive animals of the group. After amygdalectomy such interactions were overly prolonged leading to a reorganization of the dominance hierarchy (81). It was as if the amygdalectomized monkeys approached each interaction as novel. Prior experience which modulated the behavior of the control subjects seemed to have little influence after amygdalectomy. We shall have occasion to return to this finding repeatedly.

Analyses of the effects of amygdalectomy and electrical stimulations of the amygdala on avoidance (fleeing) behavior have come to a similar conclusion. Escape behavior is unaffected (59, 75) and sensitivity to shock is not diminished (5). Nor is there a change in generalization gradient to aversive stimulation (36, 37). What appears to be affected primarily is the mnemonic aspect of avoidance-the expectation that aversive stimulation will occur unless the behavior is *stopped*.

Such expectations are ordinarily referred to as "fear" but it must be clearly kept in mind that what distinguishes fear from pain (i.e., avoidance from escape) is an expectancy that stops the behavior from occurring.

The theme recurs when the effects of amygdalectomy on sexual behavior are analyzed. Hypersexuality is found to be not so much a quantitative increase in sexual behavior but an increased territory and range of situations over which the behavior is manifest (25, 57). Ordinarily cats *stop* such behavior in unfamiliar territory.

The gap between the involvement of amygdala function on the Four F's and on problem solving behavior is clearly not as great as it initially seemed. A pertinent example that has been detailed is that of so called passive avoidance which sets up a conflict between approach and avoidance behavior. After amygdalectomy animals fail to *stop* their approach on the basis of an aversive experience. Such conflict is, however, not limited to situations that involve aversive reinforcement. Approach-approach conflicts such as occur in delayed alternation partake of the same sorts of processes. Therefore, we tested amygdalectomized subjects on various forms of alternation tasks and found the monkeys with lesions to be impaired (71). Once again, the function of the amygdala is not limited to the aversive domain but rather extends wherever immediately current behavior involves *stopping* prior ongoing behavior.

The finding that the amygdala is involved in *stopping* ongoing behavior led to a series of studies on its role in the orienting reaction. This series of studies clearly showed that the visceroautonomic components of orienting were markedly affected by amygdalectomy and that the habituation of orienting was dependent on the occurrence of these visceroautonomic responses. Behavioral habituation, the indicator of familiarity, occurs in part, therefore, as a result of visceroautonomic activity. What is oriented to the novel, is a function of the familiar, the expected, on the basis of prior experience. However, the prior episode must have included a visceroautonomic reaction to be effectively experienced.

It is, of course, clear from a host of other studies relating brain and behavior, that all memory processes do not critically depend on the occurrence of visceroautonomic responses. The learning of motor skills, perceptual differentiation, rote memorization, etc. are examples where the memory mechanism operates more on the basis of simple repetition (see 61, 62 for review). Still, it is equally clear that there are occasions when memory is dependent on a "booster" that

stops ongoing behavior and derives from the importance (novel, intense, distressing, or hedonic) of the situation to the organism. It is this booster type of memory process in which the amygdala is involved.

AROUSAL, ACTIVATION, THE HYPOTHALAMUS AND BASAL GANGLIA

A precise operational definition of this involvement can be given (72). This definition is based on the studies of visceroautonomic indicators. Such studies show that amygdalectomy influences the phasic components of the indicators rather than their tonic components. The term "arousal" is commonly used to describe the organism's phasic, i.e., brief response to input as in the orienting reaction, in alerting when expectations are disconfirmed etc.

The advantage of defining arousal precisely comes when it is distinguished from other similar processes with which it is ordinarily confounded. Confusion occurs most often when the phasic and tonic reactions of organisms are lumped together. Elsewhere (72) we have reviewed in detail the evidence that tonic visceroautonomic reactions are regulated by the brain mechanisms that control the organism's readiness to respond, mechanisms which center on the basal ganglia (caudate nucleus and putamen) of the forebrain. We can therefore clearly separate, both on the basis of peripheral indicators and the brain mechanisms involved, the process of phasic arousal from that of tonic activation. Arousal is a function of a set of neural systems whose forebrain extension is the amygdala; activation is a function of a set of neural systems whose forebrain extensions are the basal ganglia.

The basal ganglia of the forebrain have, until recently, been thought of primarily as regulators of muscle tone. There is now a body of evidence which shows that the basal ganglia also control sensory input (60, 61, 62). This finding is not altogether disparate to the motor control functions of the basal ganglia since these are to a large extent affected by changes in the bias of muscle spindles, receptors that reflexly regulate muscle contraction by way of feedback.

We are now in a position to take up another experimental result which has posed explanatory difficulties for decades. When lesions are made in the region of the ventromedial nucleus of the hypothalamus, rats overeat and become obese. As noted earlier, this finding led to a series of experimental results that indicated that the ventromedial hypothalamus is a critical part of a "satiety" mechanism. Before these results were available, however, it was also shown that these

same rats would eat less than their controls and might even starve if an easily surmountable barrier were placed between them and the food. The initiation of behavior and its maintenance (stop mechanism) were dissociated. Other experiments showed that the initiation of feeding was controlled by a mechanism centered on the far-lateral region of the hypothalamus, a region devoid of neurons but rich in fiber tracts (60, 90). Recently, the far-lateral hypothalamic syndrome has been replicated by administering drugs that inhibit the formation of dopamine, the putative transmitter that characterizes the nigrostriatal basal ganglia system.

Further, it was found that excitation of the ventromedial region of the hypothalamus not only stopped eating behavior but led to the stopping of other behavior. Alerting, escape, and attack could be elicited depending on the strength of stimulation. These findings led Grossman (34) to suggest that the ventromedial hypothalamus is involved in regulating "affect" not "appetite." Affect in this instance is defined on the basis of phasic reactions to input and thus fits the definition of arousal already presented (60).

In summary, the experimental evidence falls into place when it is grouped on the one hand, according to a phasic, stop, satiety mechanism which regulates arousal; and, on the other, a tonic, start, appetitive readiness mechanism that regulates sensory and motor activation. Arousal is controlled by a neural system that includes the ventromedial hypothalamus and amygdala. Activation is controlled by the basal ganglia-in particular the nigrostriatal system whose pathways course through the far-lateral hypothalamic region.

EFFORT AND THE HIPPOCAMPUS

In addition to phasic arousal and tonic activation, a third process has been distinguished by psychophysiological analysis. This third process is also tonic but differs from the activation of readiness in that the visceroautonomic indicators are influenced in an opposite direction. Thus, during readiness heart rate decelerates while acceleration accompanies this third process which we have called "effort." Other terms that are used are chronic arousal, anxiety, and reaction to stress. Again, a detailed review and analysis of the relevant neurobehavioral and psychophysiological evidence has been performed (72) with the result that the hippocampus has been shown central to the neural systems involved in regulating "effort." In this review, effort was shown to be necessary to coordinate phasic arousal and tonic readiness in situations that invoke both processes—such as discrimination reversal

(70), alternation (76), problem-solving under distraction (18), and when reasoning depends on computable variations in the situation (14, 15, 87). A good deal is also known about how the hippocampus performs this coordinating function (70).

SOME NEUROCHEMICAL PRELIMINARIES

This has been a brief overview of the methods and results of some 30 years of neurobehavioral research. The relationship of the analysis to the problems of this conference is evident: Currently, a body of data has accumulated relating a variety of brain peptides, many of them derivatives of ACTH, to a variety of behaviors. Interestingly, the behaviors that have become involved in brain peptide research are to a large extent the same as those involved initially in amygdala research and then shown to be dependent on hypothalamic, basal ganglia, and hippocampal function as well. Thus the neural organization of the mechanisms of arousal, activation, and effort delineated by neurobehavioral and psychophysiological techniques may well be relevant to the analysis of the relationship between neurochemical and behavioral processes.

Perhaps the easiest place to start is the by now well established and dramatic finding of a dopaminergic nigrostriatal system (23, 91) which has already been discussed. The evidence has repeatedly been reviewed to the effect that dopamine is involved in the maintenance of postural readiness and motivational activation (50, 86). It is also known (e.g., King and Hoebel [43]) that assertive behavior such as predatory aggression depends on the activation of a cholinergic mechanism. Thus, it is likely that the dopamine fibers interdigitate a cholinergic matrix (25) to determine the activation level of the nervous system and the readiness of the organism.

Two other by now well known neurochemical systems are those involving serotonin and norepinephrine. A large amount of research (e.g., reviews by Jouvet [42]; Barchas et al. [6]) has related these substances to the phases of sleep-serotonin to ordinary (slow-wave) sleep and norepinephrine to paradoxical (rapid-eye-movement) sleep during which much dreaming occurs. The relationship between serotonergic and norepinephrinergic mechanisms and the amygdala, seems to be similar to that between acetylcholine (ACh) and dopamine, and the striatum of the basal ganglia. Serotonergic and norepinephrinergic systems of fibers densely innervate the amygdala, the norepinephrinergic interdigitating a serotonergic matrix (see Pribram and Isaacson [70] for review).

The regulation of sleep by the amygdala has not been quantitatively documented but sleep disturbances are commonplace immediately following amygdalectomy, the animals often falling into a torpor from which they are difficult to rouse for several days to several weeks.

However, norepinephrine has been related to a behavioral function in which the amygdala is thoroughly implicated-the effects of reinforcing events (88). Norepinephrine has also been related to orienting and affective agonistic reactions. Once again a phasic response to novelty-sensed against a background of familiarity-is norepinephrinergic, whereas "familiarity" in the guise of "territoriality" and "isolation" has been shown to some extent to be dependent on a serotonergic mechanism (see reviews by Reis [77]; and Goldstein [29]).

These data suggest that norepinephrine acts by modulating a serotonergic substrate (which is determining one or another basic condition of the organism) to produce paradoxical sleep, reinforcement, orienting to novelty and perhaps other behaviorally relevant neural events that interrupt an ongoing state. The data are not as clearly supportive of this suggestion as those that relate ACh to an assertive state that becomes modulated by the activity of dopamine to produce specific readinesses. Nonetheless, as a first approximation to the data at hand, let us hold these possible neurochemical relations in mind as a tentative model with which to analyze the mass of evidence on the behavioral neurochemistry of the polypeptides.

NEUROPEPTIDES AND THE EFFORT MECHANISM

The neurochemical evidence on ACTH related peptides leads directly to the hypothesis that they are involved in the hippocampal mechanism. To begin with, Bohus (7) and McEwen et al. (52) have shown that the hippocampal circuit (Hippocampus and septum) is the brain site most involved in the selective uptake of adrenal cortical steroids. As McEwen states:

> It is only quite recently that we have come to appreciate the role of the entire limbic brain, and not just the hypothalamus, in these endocrine-brain interactions.
>
> Our own involvement in this revelation arose from studies of the fate of injected radioactive adrenal steroids, particularly corticosterone, when they entered the brain from the blood. These studies were begun, under the impetus of recent advances in molecular biology of steroid hormone action, to look for intracellular hormone receptors in brain

> tissue. We expected to find such putative receptors in the hypothalamus, where effects of adrenal steroids on ACTH secretion have been demonstrated (12, 32). Much to our surprise, the brain region which binds the most corticosterone is not the hypothalamus but the hippocampus. (52)

Thus the receptors of adrenal cortical hormones can set the neural state which becomes modulated by ACTH related peptides. Evidence that such modulation of a corticosterone determined state involves the hippocampus has been presented in this volume by van Wimersma Greidanus and de Wied.

Second, as noted in the review by Pribram and McGuinness (72), the hippocampal circuit functions to coordinate arousal (phasic response to input) and activation (tonic readiness to respond). Thus, in any complex behavioral situation, coordination would be influenced by manipulations of this circuit-and a host of apparently conflicting results might be obtained with very slight changes in the conditions of the experiment. (The best known of such slight changes is the one-way versus two-way conditioned avoidance task (see Pribram et al. [71]; and van Wimersma Greidanus and de Wied [92]).

Further, effects on phasic and tonic processes (arousal and activation) as well as on their coordination (effort) would be expected. This expectation is borne out in the catalogue of effects of manipulations of ACTH related peptides: extinction of two-way but not one-way avoidance (13) interference with passive avoidance (45), interference with learned taste avoidance (the Garcia effect-Levine [46]), interference with discrimination reversal (81), facilitation of memory consolidation (92), facilitation of exploratory behavior and conditioning (20).

Just as in the case of manipulations of hippocampal activity, *ongoing* behavioral activity (memory consolidation, exploratory behavior) is facilitated while any *change* in behavior (two-way shuttle, passive avoidance, learned taste aversion, discrimination reversal) is interfered with. This appears initially as tilting the bias toward readiness. But as Pribram and Isaacson (70) show for hippocampal function, and Sandman's group conclude in their various contributions to this conference, such an interpretation does not hold up. In the case of hippocampal research, the initial formulation stated that after hippocampal resections, animals could not inhibit their responses (51). This interpretation foundered when such animals were shown to perform well in go/no-go alternation tasks (49, 70) and that they could withhold behavioral responses despite an increase

in reaction time when distractors were presented (16).

The most cogent analysis has been performed on discrimination reversals. Isaacson et al. (40) and Nonneman and Isaacson (56) have shown that reversal learning encompasses three stages: Extinction of the previously correct response, reversion to a position habit, and acquisition of the currently correct response. Pribram, Douglas, and Pribram (68) and Spevak and Pribram (87) have shown that hippocampally lesioned monkeys are intact with regard to both the extinction and the new acquisition phases of the reversal training experience. However, such monkeys seem to become "stuck" in the 50% reinforcement phase or in position response patterns. In short, the monkeys' behavior seems to be taken over by a relatively low variable interval schedule of reinforcement and they fail to "make the effort" to "pay attention" to the cues which would gain them a higher rate of reward. Champney et al. (10) have shown ACTH related peptides to operate on just this aspect of the reversal experience-and, in fact, have shown interactions with sex differences.

Evidence such as this makes highly plausible the hypothesis that ACTH related peptides operate on the hippocampal circuit and therefore the "effort" process. But there is more. Strand et al. (89) present direct evidence that muscle fatigue is reduced by ACTH-related neuropeptides and that this effect must be central. Pribram and McGuinness (72) in their analysis review the evidence for peripheral metabolic events that contribute to effort but could at the time show only indirect evidence for a central process devoid of peripheral concomitants (73). Strand et al.'s (89) current contribution is thus a most welcome addition.

THE PROTOCRITIC DIMENSION

The foregoing analysis and review of evidence indicates that systems of corebrain stem, basal ganglia, and limbic forebrain structures can be discerned in which neurochemical events determine to a large extent the behavioral functions that are regulated by these structures.

Regulation is in part effected by the establishment, through central receptor sensitivities, of neural representations of peripheral endocrine processes, and by direct influences on these representations of centrally active neurochemical substances. Among the many relationships between endocrines and central sensitivities some were singled out as providing sufficient evidence that a systematization relevant to this volume might be attempted. Others such as the possible central effect of insulin, the special sensitivity of the amygdala to

sex hormones were not included although they cannot be ignored in any future attempt at synthesis.

At the moment three classes of systems are discernible. One class determines specific neuromuscular and neurosensory readinesses. A second deals with the momentary cessations of ongoing behavior, cessations due to interrupting distractors, the intervention of satiety or the recurrence of reinforcing events. The third class of systems coordinates the readinesses of the organism with the processes that lead to their momentary suspension.

The proposal was made that states of specific readiness were due to a cholinergic mechanism operated upon, i.e., modulated by, dopaminergic systems. The basal ganglia are the major gross forebrain embodiments of readiness mechanism.

The gross forebrain locus upon which the systems that deal with momentary cessation of behavior converge is the amygdala. Neurochemically, these systems are posited to be basically serotonergic with norepinephrinergic operators modulating the basic serotonergic state.

Finally, a coordinating mechanism was discerned whose forebrain extension lies within the hippocampal circuit. The neurochemical constitution of this class of systems is hormonal with neuropeptides operating on the hormonally induced neural state to regulate behavior. Corticosteroids and ACTH related neuropeptides are examples of the functions of this third class of systems.

In conclusion, I would like to venture that the protocritic process-the brain organization of the pain-temperature dimension of experience-is central to these three classes of systems. As first proposed by Brobeck (9) and reviewed in detail by Grossman (33) temperature regulation anchors muscular tonicity, water metabolism, and food intake. As reported by Feldberg and Myers (22) and elaborated more recently by Myers (55), *two* reciprocal hypothalamic neurochemical mechanisms can be discerned as controlling these functions. One is a serotonin-norepinephrine mechanism (serotonin elevates and norepinephrine lowers temperature) and the other is an ACh-dopamine mechanism (ACh elevates and dopamine lowers temperature). ACh also induces drinking and the catechols induce feeding. Thus, once again, the "arousal" and "activation" systems can be separately identified. However, according to the proposal made here norepinephrine should operate on the satiety mechanism in the ventromedial hypothalamus. So far, the evidence is not clear whether the increased food intake resulting from hypothalamically injected norepinephrine does in fact result from such action. Amphetamines, usually

found to stimulate norepinephrine receptor sites in the brainstem (8) decrease appetite.

At a higher level of control are the coordinating (effort) mechanisms that utilize hormones and neuropeptides to organize behavior dependent on the smooth interaction of tonically activated sensory and motor readinesses and episodic (phasic) arousals to internal and external inputs.

The role of pain in these sets of hierarchies of controls is just beginning to be established. The discovery of a morphine-like neurosecretion (eukephalin) by Hughes (38, 39), makes it plausible to treat the regulation of pain (and itch) in homeostatic terms (see 58, 63). Further, the evidence presented by Gispen et al. (27), that ACTH and some of the related neuropeptides could serve as endogenous ligands on opiate receptors provides an initial suggestion that the pain-analgesia (effort-comfort) process may function at the coordinating (hippocampal) level of the hierarchy of controls.

POSTSCRIPT

As a postscript, I will summarize the relationship of neuropeptides to emotion. On earlier occasions I have identified emotional processes as rooted in the phasic arousal mechanisms discussed here (60, 65, 74, 94) and distinguished them from motivational processes rooted in the readiness mechanisms. The classification of arousal, activation, and effort mechanisms was developed in order to understand the effects of brain operations and recordings on attentional and intentional behavior (72). And the relationship of attention and intention to learning and remembering has been reviewed as well (58, 63). Thus the neurochemical analysis undertaken here is relevant to the topic assigned. The analysis would predict that neuropeptides would be only indirectly involved in the regulation of emotion (affect) and motivation. Only when emotional and motivational processes need be coordinated would neuropeptide manipulations show an effect. The reports presented at the conference bear out this prediction. Emotion and affect are found minimally influenced by ACTH related compounds in man (18). Conflict producing tasks such as passive avoidance (45), learned taste aversion (46), two-way shuttles (13, 92), and frustrative non-reward (31) are the instruments of choice for demonstrating the effects of neuropeptides. One-way shuttles and simple punishments show either no effect or a mild facilitation of the reinforcing process.

As in the case of emotion and motivation, the effects of neuropeptides on learning and memory consoli-

dation appear to be secondary to their coordinating role. This is brought out most clearly in the myriad of neurochemical effects of neuropeptide manipulation described in the papers dealing with these topics in this volume.

My conclusion is, therefore, that brain peptides regulate those "protocritic" processes that serve primarily to coordinate phasic arousal and tonic activation. Emotional, motivational, learning and memory processes are influenced only secondarily by neuropeptides when coordination between phasic arousal and activation is demanded. The function of the neuropeptides appears to be primarily manifest in the behavioral processes of attention and intention (decision) and in brain systems whose forebrain extension is the hippocampal circuit.

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