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THE PSYCHOPHYSIOLOGY OF ANXIETY

WITH A REVIEW OF THE LITERATURE CONCERNING ADRENALINE

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With a Review of the Literature Concerning Adrenaline

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Since the 1950s there has been a renewed interest in the psychophysiology of acute and recurrent anxiety (2, 5, 15, 30, 35, 36, 40, 47, 60, 66), especially in the psychophysiologic function of adrenaline (3, 4, 6, 7, 16, 18, 20–28, 31, 33, 34, 48, 53, 55, 57–61, 64, 65). A review of the recent literature is required to maintain perspective and to facilitate further studies. Similarly, a retrospective review of the older literature is necessary to reintegrate the theories of William James (38) and Walter B. Cannon (11–13) with the pioneer research of Tompkins *et al.* in 1919 (63) and with subsequent experimental and theoretical papers (1, 8–10, 14, 17, 19, 29, 32, 37, 39, 41–46, 49–51, 54, 56, 62).

The recent and remote literature on the psychophysiology of anxiety is reviewed and re-evaluated here on the basis of recent advances in clinical and experimental psychiatry, physiology and learning theory. Special attention is given to the function of the epinephrine fraction of adrenaline: first, in producing sympathomimetic symptoms which reinforce the acute anxiety in a self-generating fashion, and second, in producing sedative-like and parasympathomimetic effects which may counterbalance the initial stages of the anxiety.

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EPINEPHRINE SECRETION IN RESPONSE TO ANXIETY

Cannon postulated that the adrenal medulla secreted adrenaline in response to emotional excitation during fight and flight reactions to stress (11–13). Subsequent to Cannon's work, adrenaline was separated into epinephrine and norepinephrine, and attempts were made to relate these components to separate emotional states (2, 21). Ax found norepinephrine-like physiological responses associated with "anger," and a combination of epinephrine and norepinephrine-like responses associated with "fear" (2). In a much large study of normal volunteers, Funkenstein found epinephrine-like cardiovascular responses during acute fear and anxiety reactions to stress, and norepinephrine-like responses during acute anger reactions (26-28).

Independent evidence supporting Ax's and Funkenstein's concepts has come from a number of sources. Martin summarized much of this evidence in 1961 (47). Urinary epinephrine and norepinephrine levels were found to be raised during acute anxiety and anger reactions respectively (20). In addition, studies of humans undergoing gravitational stress in a space laboratory have upheld the association of high blood epinephrine levels with anxiety and high blood norepinephrine levels with anger (60). Also, preliminary studies from the same source have indicated that one can predict these physiological responses using fear and anger profiles derived from projective tests (60). Further support has come from a recent experimental study by Mason *et al.* (48). High norepinephrine blood levels in

monkeys were associated with most or all coping situations (reward and punishment), while high epinephrine blood levels were associated with only transient "uncertainty" situations involving ambiguous or ambivalent cues.

Evidence has also suggested that the organism has the biologic capacity to respond differentially to stress by secreting different proportions of epinephrine and norepinephrine. Hess has shown that fear behavior and anger behavior can be produced separately by stimulating separate areas within the hypothalamus (35, 36), while Folkow and von Euler have shown an association between fear behavior produced in this manner and a simultaneous output of adrenal medullary hormone high in epinephrine (22). In addition, epinephrine and norepinephrine have been located within separate cells of the adrenal medulla (33).

THE SYMPATHOMIMETIC EFFECTS OF EPINEPHRINE

Evidence has been presented above supporting Ax's and Funkenstein's hypothesis that a higher proportion of epinephrine than norepinephrine is secreted during the acute anxiety reaction. It is now known that the epinephrine fraction of adrenaline is also more potent than norepinephrine in producing the sympathomimetic symptoms characteristic of anxiety (34, 55, 61).[2]

The role of these epinephrine-induced sympathomimetic symptoms has long been a point of controversy. James originally postulated that these symptoms actually caused or elicited the anxiety (38). While Cannon believed these symptoms were primarily a response to the anxiety (11–13), he also noted that the injection of adrenaline, activating sympathomimetic symptoms, could elicit further anxiety in exceedingly anxious subjects (12, 46). In the language of learning theory, Cannon's observation can be restated and reinterpreted as follows: because of the learned association between sympathomimetic symptoms and anxiety in the recurrently anxious person, adrenaline-induced sympathomimetic symptoms can reinforce further anxiety. That is, the individual becomes conditioned so that the symptoms of anxiety elicit or reinforce further anxiety.

In 1919 Tompkins, Sturgis and Wearn first demonstrated that adrenaline could elicit anxiety in previously conditioned or "neurotic" subjects (63). These investigators tested the effect of intramuscular adrenaline (5.0 mg, largely epinephrine) upon army recruits suffering from the "irritable heart" syndrome, an acute anxiety reaction characterized by cardiovascular instability, dizziness and fatigue during stress. They found that recurrently anxious or "neurotic" recruits responded to adrenaline injection with the symptoms characteristic of their acute anxiety reactions, including both the subjective psychologic symptoms and the more objective physiologic signs. The normal controls reported no psychologic symptoms and demonstrated milder physiologic changes in response to adrenaline injection.

Much of the subsequent literature concerning the effect of injected adrenaline can be clarified retrospectively on the basis of this variable: the strength of the previously learned association between acute anxiety and symptoms of sympathomimetic activation. This learned association determines the degree to which the adrenaline-induced symptoms or cues will reinforce the individual's anxiety. Its strength can be estimated from the patient's account of his past anxiety reactions and associated symptomatology. For example, Lindemann and Finesinger found that individuals with a past history of recurrent, intense anxiety accompanied by *para*sympathomimetic

[2] In studies carried out before the availability of crystalline epinephrine, adrenaline was used. This mixture was largely epinephrine (85% or more), and so for most purposes the adrenaline studies are analogous to more recent epinephrine studies.

symptoms responded with acute anxiety to *para*sympathomimetic drugs, but not to sympathomimetic drugs (44). In contrast, individuals with a past history of intense anxiety associated with sympathomimetic symptoms responded with acute anxiety to sympathomimetic drugs, but not to parasympathomimetic drugs. Thorley reported that a combination of the two drugs elicited anxiety in an individual whose past anxiety symptoms had both sympatho- and parasympathomimetic components (62). There is even some equivocal evidence that past conditioning is so important a variable that an emotion other than anxiety can be elicited by adrenaline injection if that emotion has been associated with adrenaline injection or sympathomimetic symptoms in the past (46, 54, 62).

The anxiety reactions elicited by adrenaline are not simply exaggerated physiologic responses to the drugs. They have included subjective symptoms as varied and complex as those found clinically in the spectrum of acute anxiety reactions (4, 8, 14, 41, 44, 45, 54, 56, 62, 63), including, for example, both psychogenic physical symptoms completely unrelated to any drug effect (41), and reactivation of a painful childhood memory (34). The importance of the variable, past conditioning, has been obscured because most recent studies have not used "normal" or unconditioned subjects. However, even in "normal populations" occasional subjects turn out to have a past history of repeated sympathomimetic anxiety reactions and react strongly to the drug (4, 34).

When the past conditioning of internal cues is taken into account, some differences in the results of various experiments still remain unexplained. Most of these differences can be accounted for by a second variable: the degree to which the experimental environment or the external cues reinforce anxiety. This second variable must be separated out by inference, since there are very few studies which attempt to control the environment. For example, the presence or absence of a psychiatric interviewer is an important variable which has not been controlled, but which seems significant in several studies. Frankenhauser and Jarpe elicited very little anxiety with intravenous infusions of 3–12 mcg/kg/hour of epinephrine (24). They noted the absence of a psychiatrist during the experiment and wondered if they thereby failed to appreciate the presence of anxiety in their subjects. In contrast, Basowitz *et al.* elicited somewhat more anxiety in the presence of psychiatrists with infusions of 5 mcg/kg/hour (4). Most likely, however, the psychiatrists were needed not so much to perceive the anxiety, as to reinforce it by their presence. Thus Hawkins *et al.* reported relatively little anxiety in their subjects, a team of psychiatrists who alternated as observers and subjects (34). These trained observers would presumably have perceived any anxiety, but they might not have reinforced anxiety among themselves. Pollin *et al.* evoked the most severe anxiety in normal subjects (53). With infusions of 9 mcg/kg/hour, they produced numerous symptoms, including withdrawal and disruption of communication. This greater emotional response probably resulted from a complex of environmental cues which by itself elicited verbalized anxiety before the epinephrine was administered. The cues included a difficult intra-arterial cannulation, awe-inspiring monitoring apparatus and a large number of observers, including psychiatrists. The results were in marked contrast to the relatively little anxiety elicited by Frankenhauser and Jarpe, who used even larger doses of epinephrine with some subjects, but who conducted the experiment in a much less anxiety-provoking environment (23).

Another set of experiments with "normal subjects" given intramuscular adrenaline illustrates the importance of environmental cues (14, 19). No emotion or "cold emotion" was elicited by Cantril and Hunt

(14). Their subjects were students and professional people, there were no anxiety-provoking environmental cues other than the injection, and the investigators apparently did not anticipate anything dramatic or startling. In contrast, "some degree of anxiety, apprehension or fear" was evoked in each "normal control subject" by Dynes and Tod (19). Their subjects were two hospitalized patients recovering from hernia operations and four convalescing from tuberculosis of the bone. Blood samples were drawn and physical exams performed on each subject during the experiment, and the investigators seemed to expect a significant response from the subjects. Merely being a patient in a hospital setting subjected to an "experiment" was probably sufficient to reinforce anxiety in these subjects, without the additional procedures and the expectations of the experimenters.

Future studies may demonstrate an even more dominant role for environmental cues than might be inferred from these uncontrolled studies. Recently, Schacter and Wheeler (57) and Schacter and Singer (58) have conducted what appear to be the only experiments in which environmental cues have been adequately controlled. They have shown that appropriate environmental cues can influence the subjects to interpret adrenaline-induced excitation as emotions other than anxiety.

As might be expected, anxiety reactions associated with administration of adrenaline have been most severe when both variables have been strong. That is, the anxiety reactions have been greatest when the subjects have reported past histories of recurrent severe anxiety reactions with sympathomimetic symptoms, and when the environmental cues in the experimental setting were also strongly associated with anxiety. For example, Lindemann and Finesinger reported marked anxiety reactions when acutely anxious patients with known histories of sympathomimetic symptoms were given intramuscular adrenaline during one of a series of psychiatric interviews (44, 45).

The literature can now be collated on the basis of these two variables. The first group of articles cited includes studies in which the subjects given adrenaline did not experience intense or "real" anxiety according to their own reports and according to observations by the experimenters. In this group, the subjects did not have histories of severe, repeated anxiety reactions, and the experimental conditions were relatively free of anxiety-provoking cues (4, 14, 19, 23–25, 39, 41–43, 46, 54, 57, 58, 61, 63). The second group includes studies in which the subjects given adrenaline did experience intense anxiety. In these studies the subjects who developed acute anxiety had a past history of recurrent anxiety reactions with sympathomimetic symptoms (4, 8–10, 34, 41, 44–46, 54, 56–58, 62, 63), or the experimental conditions were sufficiently stressful to reinforce anxiety responses (19, 46, 53). Epinephrine, which is secreted in larger amounts than norepinephrine during anxiety responses (2, 20–22, 26–28, 47, 48, 60), activates the sympathomimetic symptoms characteristic of anxiety, and is thereby more potent in eliciting experimental anxiety (34, 55, 61).

An important clinical inference can be drawn from this review. Sympathomimetic symptoms of anxiety are both a response to the central nervous system state of anxiety (as Cannon postulated) and a reinforcement of further anxiety (as James postulated). The acute anxiety reaction can become self-generating, since the symptoms of the anxiety reaction can reinforce the reaction, causing it to spiral. Similarly, each separate anxiety reaction can further condition the individual to respond in the future to his own internal cues with more intense anxiety reactions. Epinephrine, the dominant fraction of adrenaline during anxiety reactions, is more potent than norepinephrine in activating the sympathomimetic symptoms which reinforce the

anxiety. Thus epinephrine plays a major role in determining the self-generating character of acute anxiety reactions. This has important theoretic and therapeutic implications for those well-documented anxiety syndromes which so closely resemble drug-induced anxiety reactions (15, 49, 63, 66).

PARASYMPATHOMIMETIC AND SEDATIVE-LIKE EFFECTS OF EPINEPHRINE

Thus far it has been asserted that adrenaline-induced sympathomimetic symptoms can elicit and reinforce anxiety in appropriately conditioned individuals. In evaluating the possible role of adrenaline in clinical anxiety reactions, it is necessary to consider two lesser-known effects of adrenaline: 1) compensatory parasympathetic nervous system hyperactivation; and 2) a sedative-like or fatigue-like reaction.

Compensatory parasympathotonia has been clinically described as a delayed response to initial sympathotonia in acute anxiety (49), and as a response to prolonged intravenous injections of adrenaline (9). Gellhorn and Miller have recently attempted to categorize patients according to the degree of the parasympathomimetic response following the injection of norepinephrine (31). Darrow and Gellhorn have described a decreased responsiveness to endogenous adrenal medullary secretions in cats (17), which may be partially caused by compensatory parasympathetic hyperactivation.

The sedative-like effect has not been sufficiently studied to distinguish fully between sedation, fatigue, psychomotor retardation, and even general analgesia. Previous studies have demonstrated a sedative-like effect following direct instillation of adrenaline into the central nervous system (55, 59). Two recent studies have attempted to measure this effect following systemic intravenous (59) and intramuscular administration (6). Breggin reported that 75–100 mcg of adrenaline in oil, when administered intramuscularly to rats, produced somnolence, loss of muscular tonus, weakness, and relative unresponsiveness to loud noises, jolts, and toe pinching. The effect became obvious within fifteen to thirty minutes in animals given 50 mcg or more, and lasted for several hours. Approach behavior after food deprivation was abolished by 100 mcg, but unaffected by 25 mcg of adrenaline in oil intramuscularly. Smaller doses of 10–40 mcg produced a statistically significant dose-dependent decrement in exploratory runway behavior.

To relate the behavioral effects to physiologic changes, several animals were implanted with permanent EKG electrodes, allowing the recording of their heart rates without further restraint. All four animals given 100 mcg maintained a tachycardia more than two hours after the drug injection (when the experiment was arbitrarily terminated), and three showed a relative bradycardia during that time, indicating a compensatory parasympathotonia. The one animal injected with 25 mcg showed a significant thirty-minute tachycardia; the two animals injected with 15 mcg showed no change in heart rate. Thus the doses of intramuscular adrenaline in oil which caused marked sedative-like effects also produced prolonged physiologic effects, including parasympathotonia. The long duration of action of the drug indicated that relatively low blood levels were responsible for the behavioral and physiologic effects.

Another study of the sedative-like effect following systemic administration was that of Sharpless (59), who demonstrated what he called "stupification" in cats after continuous thirty-minute infusions of epinephrine at the rate of 2 mcg/kg/min. The stupification was measurable as a depression in an approach conditioned reflex. Somewhat higher doses produced somnolence, as well as vomiting, and an EEG pattern typical of drowsiness. Epinephrine was more potent in producing these effects than norepinephrine.

A sedative-like effect has been noted as

an occasional side-effect or symptom in human subjects following the prolonged intravenous infusion of epinephrine (4, 10, 53). Transient, infrequent fatigue effects have been noted after single intramuscular injections (39, 45). Generally, this finding has not been emphasized and has not been related to the sedative-like effect recently studied in laboratory animals or to the clinical symptom of fatigue in recurrent or prolonged anxiety. In another experiment involving large intravenous infusions no reference was made to sedation or fatigue (34), and in still another it was noted to be absent (24). No explanation is apparent for this discrepancy, but it may be important that the two negative experiments also produced only relatively mild anxiety responses in most of their subjects.

The mechanism of any sedative-like or compensatory parasympathotonic effect may be through a direct action on the central nervous system. Rothballer has summarized a number of central nervous system effects of adrenaline (55), and Ivy has demonstrated a general analgesia of central nervous system origin following the systemic administration of adrenaline in man (37). Thus there is considerable evidence that adrenaline can affect the central nervous system. Sharpless has postulated that the sedative-like effect is central, since it has been reproduced by the instillation of epinephrine directly into the brain (59). There is also evidence that the parasympathomimetic response to norepinephrine is central in origin (31).

If this sedative-like effect is central in origin, it is probably mediated by the hypothalamus, since systemically administered adrenaline accumulates only in this region of the brain (3, 65). In addition, the highest concentration of endogenous central nervous system adrenaline is in the hypothalamus (64).

The possibility that adrenaline may act upon the hypothalamus to produce a sedative-like and parasympathotonic effect suggests a further speculation that adrenaline activates Hess's (7, 35, 36) trophotropic function of the hypothalamus. According to Hess's model, the hypothalamus has separate "centers" or, more accurately, separate functions: the ergotropic, which controls arousal and sympathotonia, and the trophotropic, which controls sedation and parasympathotonia. The possibility that adrenaline may act as a hormonal feedback mediator from the ergotropic to the trophotropic functions of the hypothalamus is consistent with the data: adrenaline is secreted from the adrenal medulla during ergotropic activation; it can cross the blood-brain barrier in the region of the hypothalamus; and it can elicit sedative-like and parasympathotonic effects which are controlled by the hypothalamus. This proposed adrenaline feedback mechanism would function in a similar fashion to other feedback mechanisms, leading to compensatory changes (sedation and parasympathotonia) which counterbalance or antagonize the original state (arousal and sympathotonia).

The reader is referred to Rothballer's review to place this new speculation in the context of other possible mechanisms for the sedative-like effect (55). Without going deeply into the problem, the obvious issue of the paradoxical effect of adrenaline should be noted, namely, that small amounts of adrenaline produce "arousal" and larger amounts produce sedation (55). It seems plausible that the arousal effect of adrenaline is a conditioned or learned response to the sympathomimetic cues evoked by adrenaline (6), much as anxiety may be a conditioned response to these cues (as described above). Thus the smaller doses of adrenaline may activate the peripheral nervous system, thereby alerting the animal and raising its level of anxiety or arousal, while the larger doses affect the central nervous system directly to produce sedative-like and parasympathotonic effects.[3]

[3] The distinction between "anxiety" and "arousal" (5) is too complex for analysis here, except to point out that each may be treated similarly

The greatest defect in the adrenaline feedback hypothesis concerns the somewhat large doses required to achieve the sedative-like effect, *e.g.*, 10–20 mcg of adrenaline intramuscularly in oil in rats (6), 2 mcg/kg/min of epinephrine intravenously in cats (59), and less frequently and less dramatically 5 mcg/kg/hour intravenously in humans (4). Further investigations are needed to determine, for example, if less than 10 mcg of adrenaline in oil intramuscularly can affect other forms of rat behavior, and to determine how closely such injections mimic physiologic conditions. In humans, one study indicates a *resting* adrenal medullary secretion rate of 0.6 mcg/kg/hour (16) as compared to the experimental dose rate of 5.0 mcg/kg/hour used by Basowitz *et al.* (4). It is difficult to draw inferences from this paucity of data. Sharpless has pointed out, however, that small endogenous secretions of adrenaline within the central nervous system itself might produce sedative-like effects without achieving a high systemic blood level of adrenaline (59). Vogt has shown that any drug which activates the hypothalamus to stimulate secretion from the adrenal medulla also depletes the hypothalamus of adrenaline (64), which would support the alternative hypothesis that ergotropic activation of the hypothalamus leads to a liberation of adrenaline within the hypothalamus itself, permitting a redistribution of the hormone to other nearby sites, such as the regions which control the trophotropic functions.

The model of an adrenaline feedback is especially consistent with Misch's observation (49) that acute anxiety occurs in two phases—the acute arousal state with sympathomimetic symptoms (Hess's ergotropic activation), followed by the sedated or fatigued state with parasympathomimetic symptoms (Hess's trophotropic activation). By separating out two competing hypothalamic systems to account for mood instability and autonomic nervous system instability, this model suggests many experimental approaches to the complex unstable symptoms of acute and recurrent anxiety (15, 48–50, 63, 66). This approach is also consistent with the concepts proposed in the present paper concerning the function of sympathomimetic symptoms in reinforcing anxiety. It describes physiologic changes which accompany and counterbalance the psychologic changes during acute and recurrent anxiety.

in this model. Adrenaline-induced sympathomimetic cues can produce either arousal or anxiety, depending upon the definition of these terms, and depending upon certain experimental variables, such as whether or not the individual has learned to associate sympathomimetic cues with painful or anxiety-provoking past experiences.

DISCUSSION

This review of the literature calls attention to or introduces several specific hypotheses about the psychophysiology of anxiety, with special emphasis on the function of adrenaline. Each hypothesis is operationally defined and subject to experimental investigation. Together they make up an internally consistent model for the psychophysiology of anxiety which accounts for most of the data available in the literature and for many observations in clinical experience.

The hypotheses and their implications are as follows:

1) *The proportion of epinephrine secreted by the adrenal medulla during anxiety is greater than during other responses, such as anger.*

2) *The sympathomimetic cues or symptoms produced by epinephrine during anxiety become learned in association with the anxiety.* The symptoms can then elicit or reinforce further anxiety, producing a self-generating, spiraling anxiety reaction. Similarly, each recurrent anxiety reaction strengthens the conditioned association between anxiety and its sympathomimetic symptoms, thereby increasing the intensity of future anxiety reactions.

3) *Prolonged high blood levels of epinephrine produce fatigue or sedative-like effects and parasympathomimetic effects through a feedback of adrenaline hormone to the hypothalamic trophotropic functions.* Thus the peripheral sympathomimetic effects of adrenaline, which reinforce anxiety, are antagonized by the central nervous system response to adrenaline.

From these hypotheses it is apparent that epinephrine may play a key role in producing the clinical difference between anxiety and other responses, such as anger: epinephrine is secreted in a higher proportion during anxiety (Hypothesis 1), and epinephrine is more potent in producing sympathomimetic cues which further generate the anxiety (Hypothesis 2) and is more potent in producing parasympathomimetic cues and sedative-like effects which eventually counterbalance the initial stages of the anxiety (Hypothesis 3).

Each of these hypotheses can be subdivided into several hypotheses for the purpose of experimentation, and each raises complex issues. The first hypothesis assumes not only a significant physiologic difference between anxiety and anger, but also a significant psychologic difference. In actual practice the "pure anxiety reaction" is rarely seen, and anxiety is often difficult to distinguish from anger and other affective states. This paper focuses more on physiologic differentiation than on the psychologic.

The second hypothesis, that sympathomimetic cues reinforce anxiety, has been inferred from studies involving the injection of adrenaline. It will be more difficult to study the role of sympathomimetic cues in clinical anxiety reactions precipitated by environmental cues alone rather than by adrenaline injection. The hypothesis also involves a massive oversimplification of the individual's complex perceptual relationship to his own body, *i.e.*, it assumes a one-to-one correlation between the physiologic events (end-organ activation by adrenaline) and the perceived events (the symptoms). Similarly, it leaves out numerous clinically described phenomena, such as those subsumed under "defense mechanisms."

The third hypothesis, that adrenaline functions as a hormonal feedback to the hypothalamus producing sedation and parasympathotonia, will be difficult to test in human subjects under clinical conditions. It should be considerably easier to study the effect in animals, but possibly the effect observed in animals may not be analogous to the subjective symptoms of fatigue reported in humans. Furthermore, it will not be easy to distinguish between psychomotor retardation, tranquilization, sedation and general analgesia. Hess's postulate that the sedation and parasympathotonia are related functions of the hypothalamus is also subject to further investigation. Despite all these reservations, the adrenaline feedback hypothesis does explain most of the meager data available, and it warrants further consideration for its heuristic value.

SUMMARY

The recent and remote literature on the psychophysiology of anxiety has been reviewed and re-evaluated on the basis of recent advances in clinical and experimental psychiatry, physiology and learning theory. Operational hypotheses have been set forth relating the experimental data to the clinical phenomena, with special attention to the role of epinephrine (adrenaline).

The first section reviewed the evidence that anxiety responses produce a relatively higher proportion of epinephrine than norepinephrine from the adrenal medulla. The next section cited literature concerning the response of "normal" and "neurotic" subjects to the injection of epinephrine. Apparently conflicting data are accounted for by two variables: first, the strength of the subject's previously learned association between acute anxiety and sympathomi-

metic symptoms, and second, the degree of current anxiety reinforcement in the experimental setting. It was suggested that the sympathomimetic symptoms produced by epinephrine during anxiety further reinforce the individual's anxiety, evoking a self-generating, spiraling anxiety reaction. A third section presented some very recent experiments which demonstrate sedative-like and parasympathetic effects following the systemic administration of epinephrine. It is postulated that epinephrine may function as a hormonal feedback mediator to the trophotropic function of the hypothalamus (Hess), producing the sedative-like and parasympathetic symptoms found in intense or prolonged anxiety.

Thus the initial adrenal medullary secretion during anxiety may evoke sympathomimetic symptoms or cues which further reinforce the anxiety response, while more prolonged secretion may evoke parasympathetic and fatigue or sedative-like effects which compensate for the initial stages of the anxiety. Since epinephrine is a more prominent secretion in anxiety than in other responses, such as anger, and since it is more potent in producing sympathomimetic and subsequent sedative-like effects, epinephrine may account for many of the clinical phenomena characteristic of anxiety.

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