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(6) STRESS, ADRENOCORTICAL HORMONES, AND PERFORMANCE.

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Behavioral and Physiological Studies of Stress:
The Pituitary-Adrenal System and Behavior

During the years of support of this research by the Office of Naval Research three major areas of investigation were undertaken and completed with resulting publications. These three areas are:

1. Pituitary-adrenal system and behavior,
2. Environmental influences on pituitary-adrenal activity,
3. Expectancy and coping.

1. Pituitary-Adrenal System and Behavior

It has now become apparent that the pituitary-adrenal system, in addition to its other adaptive functions with regard to tissue repair and metabolic changes during emergency situations, also has a major effect on behavior. Indeed, both the pituitary peptide, ACTH, and the secretions from the adrenal have specific influences on a variety of behavioral processes.

The studies conducted under this area attempted to investigate the particular role of ACTH on certain aspects of behavior. These studies investigated two behavioral systems: (1) the effects of ACTH on learning under aversive stimulation, and (2) the effects of ACTH on learning of appetitive conditions. It was found that ACTH does indeed affect learning of passive avoidance in mice. In this particular study, male A/Jax mice learned a passive avoidance significantly faster than males of another strain (DBA/2). The A/Jax mice also showed a significantly greater increase in plasma corticosterone following the passive avoidance tasks than the DBA/2 animals. However, when both groups were pretreated with dexamethasone the DBA/2 passive avoidance behavior was unaffected, whereas the dexamethasone-treated A/Jax animals were retarded in the acquisition of the avoidance response and thus became equivalent to the DBA/2 mice. These results were interpreted as indicating that ACTH had an important influence on the acquisition of an avoidance response. This was one of the first demonstrations that ACTH actually could affect the acquisition of an avoidance response as opposed to numerous studies which have indicated that ACTH could indeed affect the retention of an avoidance response.

In a subsequent study in rats it was further demonstrated that ACTH, once again, could affect both the acquisition of a passive avoidance response and the retention of an avoidance response as measured by extinction. Thus, in a passive avoidance task in rats it was demonstrated that even a single injection of ACTH given 10 minutes before a punishment trial significantly strengthened the passive avoidance response acquired on that trial. Clearly, this observation that a single injection of ACTH on the punishment trial required to produce prolonged passive avoidance response is again best interpreted as an acquisition effect. In this particular experiment we also demonstrated once again that ACTH does have an effect on extinction.

In almost all of the studies in the literature on the effects of ACTH on behavior most of the learning tasks have involved some form of noxious stimulation. In order to test the generality of the ACTH effects on both learning and retention, animals were tested in a leverpress situation for water. Animals given ACTH tended to acquire the lever response more rapidly and in addition, animals given ACTH during extinction tend to show a greater resistance to extinction, although this effect was somewhat transitory.

These studies have added to the body of information which demonstrates that not only does ACTH have an effect on retention as measured by extinction, but also an effect upon the acquisition and learning of a number of behavioral tasks.

Published papers related to the above section:

Conner, R.L. and S. Levine. The effects of adrenal hormones on the acquisition of signaled avoidance behavior. Hormones and Behavior 1: 73-83, 1969.

Levine, S. Hormones and conditioning. In Nebraska Symposium on Motivation, 1968, W.J. Arnold (Ed.). Lincoln, Neb.: University of Nebraska Press, 1968. Pp. 85-101.

Levine, S. and R. Levin. Pituitary-adrenal influences on passive avoidance in two inbred strains of mice. Hormones and Behavior 1: 105-110, 1970.

Guth, S., J.P. Seward and S. Levine. Differential manipulation of passive avoidance by exogenous ACTH. Hormones and Behavior 2: 127-138, 1971.

Guth, S., S. Levine and J.P. Seward. Appetitive acquisition and extinction effects with exogenous ACTH. Physiology and Behavior 7: 195-200, 1971.

2. Environmental Influences on Pituitary-Adrenal Activity

A. Preshock

Prior exposure to intense unsignaled and inescapable electric shock has been shown to alter subsequent behavior of rats in the presence of novel or aversive stimulation. Within this program a number of experiments were undertaken and completed which studied the influence of inescapable noxious stimulation on various parameters of the pituitary-adrenal system and other psychophysiological responses to stress.

In the initial study the adrenocortical response and passive avoidance behavior was studied in rats that had been exposed to preshock. Previously shocked animals exhibited a much greater pituitary-adrenal response to mild shock than did non-preshocked animals, and in addition, passive avoidance was markedly facilitated. However, since the preshocked animals had had a signiicant experience in the presence of aversive stimulation, we questioned the generality of these findings of changes in adrenocortical response to shock. Animals were therefore tested in a completely neutral situation - the open field - and pituitary-adrenal response to mild, novel stimulation was examined. It was found that, here again, preshocked animals tended to respond significantly higher to novel stimulation not related to shock and it therefore appears that experience with prior aversive stimulation creates some generalized effect which carries over to other conditions which could not be attributed to learning.

In a further investigation the heart rate response to the open field was compared between rats which had been preshocked and controls. The results indicated that control animals showed a steady increase in heart rate across a 3-minute exposure of 4 days of testing, while preshocked animals showed a marked initial heart rate deceleration followed by a partial recovery each day. The heart rate response of the preshocked animals to the open field was not related to any heart rate response to shock during the preshock treatment and the heart rate responses of both preshocked and control animals were specific to the open field situation with both groups showing steady heart rate deceleration across 3 minutes after being placed in their own cages. The results indicated that there is indeed an altered perception of environmental change produced by preshock and that the preshocked animals were indeed more responsive by both hormonal and autonomic responses to novel situations.

It should be indicated however that in a series of subsequent experiments we have found that the response to preshock and its subsequent effects can be markedly ameliorated if the animals are permitted to fight in response to shock and although the fighting does not appear in any way to alleviate the experience of shock, it does apparently alter the perception of the animals, and the subsequent deleterious effects of preshock are often eliminated if the animals are permitted to fight in response to the shock stimulus.

B. Circadian Rhythmicity and Suppression of Pituitary-Adrenal Activity

While the studies on preshock were designed to examine the influence of a set of conditions which chronically alter stress responsivity, we have, in another series of experiments, examined another environmental influence on pituitary-adrenal activity.

Rats, normally, have a circadian rhythm of pituitary-adrenal activity which is characterized by low basal values in the morning and high basal values late in the afternoon. In an initial series of experiments it was determined that this circadian rhythm could be markedly altered if the animals were placed on a restricted food or water intake so that the time of feeding or drinking occurred in the a.m. rather than in the p.m. If this occurs, the peak of adrenocortical activity now occurs prior to the onset of feeding or watering and the afternoon values are strikingly suppressed. However, in another study, it was demonstrated that rats having access to food and water for 1 hour daily showed, again, the elevated plasma corticosterone levels prior to feeding and drinking. The activity of the pituitary-adrenal system in this experiment was studied in animals receiving food and water, food or water alone, or an empty drinking bottle. Within 5 minutes there was a 35% drop in the concentration of plasma corticosterone following each of these conditions. The decline reached 50% by 10 minutes. In those animals which received water alone or the empty drinking tube the time course was biphasic; thus following the initial drop the pituitary-adrenal system was activated. It appears therefore that the rapid suppression of the pituitary-adrenal system can occur and can be conditioned to the stimuli associated with prior reinforcement. This rapid drop seen following reinforcement has been replicated in another series of experiments. Thus, if the feeding and watering occur in the late afternoon, the peak of circadian rhythmicity is not altered; however, a similar rapid drop occurs following reinforcement.

These data raise interesting questions concerning the half-life of plasma corticosterone and there is a major question as to why steroids drop so rapidly in this situation whereas the half-life has been reported to be approximately 20 minutes. This question has been under investigation in our laboratory.

In general the results of these studies, in addition to studies to be described in the next section, have clearly demonstrated that the pituitary-adrenal system is bidirectional and responds to environmental stimuli, not only in terms of striking increments, but also can show marked suppression.

Published papers related to the above section:

Smith, E.R., J. Johnson, R.F. Weick, S. Levine and J.M. Davidson. Inhibition of the reproductive system in immature rats by intracerebral implantation of cortisol. Neuroendocrinology 8: 94-106, 1971.

Stern, J.M., M.S. Erskine and S. Levine. Dissociation of open-field behavior and pituitary-adrenal function. Hormones and Behavior 4: 149-162, 1973.

Johnson, J.T. and S. Levine. Influence of water deprivation on adrenocortical rhythms. Neuroendocrinology 11: 268-273, 1973.

Smith, E.R., R. Dominguez and S. Levine. Effects of water restriction on reproductive function in female rats. Neuroendocrinology 12: 41-51, 1973.

Erskine, M.S. and S. Levine. Suppression of pituitary-adrenal activity and shock-induced fighting in rats. Physiology and Behavior 11: 787-790, 1973.

Chalmers, D.V., S. Coyle and S. Levine. Effects of prior aversive stimulation on heart rate responses to open field exposure in the rat. Physiology and Behavior 14: 13-16, 1975.

Levine, S. and G.D. Coover. Environmental control of suppression of the pituitary-adrenal system. Physiology and Behavior 17: 35-37, 1976.

3. Expectancy and Coping

During the period of time in which ONR supported this research we believe that major strides have been taken in attempting to understand the basic concepts of stress. In a series of experiments the influences of changes in expectancy on the pituitary-adrenal was examined. Using operant conditioning procedures, it was demonstrated that extinction (nonreinforcement) following continuous reinforcement resulted in a marked increase in pituitary-adrenal activity. Thus, it was demonstrated that even though there was no aversive or noxious stimulation, an environmental change in the nature of altering the prior expectancies of the organism could indeed result in a major change in the pituitary-adrenal system similar to that observed under most traditional aversive procedures. However, further experiments demonstrated that the pituitary-adrenal system can respond bidirectionally, activation of the system is observed, and the frequency of reinforcements is suddenly less than that obtained during training. Suppression is seen if reinforcement frequencies are suddenly greater than expected. Thus it appears that there are mechanisms within the central nervous system that can process information concerning reinforcement and either activate or inhibit the controlling systems which regulate pituitary-adrenal activity.

It was further demonstrated that pituitary-adrenal responses during avoidance conditioning also demonstrate a reduction in the activation of the system when expectancies are developed and a reactivation when these expectancies are not fulfilled during extinction. Thus, if one follows the activity of the pituitary-adrenal system during the course of avoidance conditioning, what is observed is an initial high pituitary-adrenal response which is subsequently followed by a reduction in this response as the organism learns the contingencies in the avoidance learning environment. The absence of shock does not appear to be the critical dimension since even animals that do not learn to avoid, but escape, in the presence of a conditioned stimulus (feedback signal) also show a similar reduction in pituitary-adrenal activity. A theory, therefore, was developed from these data which, simply stated, is that the pituitary-adrenal activity may be suppressed when expectancies of reward are exceeded or when the animal is reinforced, while failure to meet expectancies may be one of the primary environmental conditions which increases arousal and results in increased secretion of ACTH from the pituitary.

This major finding of changes in pituitary-adrenal activity following avoidance learning was used to examine the influence of various brain mechanisms, particularly lesions in the limbic system, on the changes in internal state of pituitary-adrenal system during avoidance conditioning. It has been shown that many limbic structures are necessary for normal emotional behavior and avoidance learning. Several anatomical and physiological mechanisms may be involved. It appeared that plasma corticosterone levels following an avoidance session could differentiate between some of the avoidance deficits which are observed when certain limbic system lesions are made. Thus, basolateral amygdala lesions in rats reduced two-way active avoidance. There were also behavioral indications of less fear and plasma corticosterone levels were lower than in normals following the first day of avoidance training. Basal levels and post-ether stress levels were not changed. Further, rats with small lesions in the cingulate cortex show normal avoidance learning but not the normal decrement in plasma corticosterone observed in intact rats when an avoidance habit is overtrained. It is possible that the avoidance deficit observed in rats with large cingulate lesions is due to a loss of the fear-reducing effect of adequate behavior. Finally, rats with septal lesions also showed no change in basal levels or post-ether stress levels or post-session levels of corticosterone on Day 1. However, since rats with septal lesions showed dramatically rapid two-way avoidance conditioning, the changes in plasma corticosterone were also more rapid than observed in normal animals.

These data do present a different version of the concept of stress than had been generally accepted in the literature based on the early work of Hans Selye and are consistent with other positions which indicated that the primary activator of the pituitary-adrenal system may be some state of arousal induced by discrepancies between the external environment and the organism's perception of that environment. Thus stress becomes essentially a psychological concept rather than a concept based primarily on physical damage and injury. The relationship between the hormones elicited under conditions of stress and behavior was discussed earlier in this report.

We are indeed grateful to the Office of Naval Research for their continued support of this research and feel that there have been some major developments that emerged from the research findings. The findings related to coping and behavior were ultimately placed in a human context. An extensive study done in collaboration with Dr. Holger Ursin at the University of Bergen took the theoretical concepts and the model of expectancy and coping and studied a population of Norwegian soldiers going through parachute training. It was found that the animal models could indeed be directly applied to humans and that changes in physiological response systems could be clearly demonstrated as a function of developing expectancies in a novel and traumatic situation that is an integral part of parachute training. These results are now being prepared in a volume which will be entitled "Coping Men - A Study of Human Psychobiology".

Published papers related to the above section:

Coover, G.D., L. Goldman and S. Levine. Plasma corticosterone levels during extinction of a lever-press response in hippocampectomized rats. Physiology and Behavior 7: 727-732, 1971.

Levine, S., L. Goldman and G.D. Coover. Expectancy and the pituitary-adrenal system. In Physiology, Emotion & Psychosomatic Illness, Ciba Foundation Symposium 8, R. Porter and J. Knight (Eds.). Amsterdam: Elsevier, 1972. Pp. 281-296.

Coover, G.D. and S. Levine. Auditory startle response of hippocampectomized rats. Physiology and Behavior 9: 75-77, 1972.

Coover, G.D., H. Ursin and S. Levine. Corticosterone and avoidance in rats with basolateral amygdala lesions. Journal of Comparative and Physiological Psychology 85: 111-122, 1973.

Coover, G., H. Ursin and S. Levine. Corticosterone levels during avoidance learning in rats with cingulate lesions suggest an instrumental reinforcement deficit. Journal of Comparative and Physiological Psychology 87: 970-977, 1974.

Ursin, H., G.D. Coover, C. Køhler, M. Deryck, T. Sagvolden and S. Levine. Limbic structures and behavior: Endocrine correlates. Progress in Brain Research 42: 263-274, 1975.