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ANIMAL MODELS FOR THE NEUROBIOLOGY OF TRAUMA

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Recent clinical studies suggest that some individuals exposed to extreme stress develop long-term changes in specific brain systems. Clinical studies in this area have practical limitations, making the use of animal models essential. The animal model of inescapable stress mimics the exposure to extreme stress seen in patients with PTSD. Animals exposed to inescapable stress develop specific behavioral changes including deficits of memory, learned helplessness, and conditioned fear responses to stressors, which are associated with long-term changes in multiple neurobiological systems. This model has proven useful in the study of the neurobiological and behavioral consequences of trauma. In this issue we review animal models and preclinical research on the neurobiology of trauma.

In 1967 Seligman and Maier noted that beagles exposed to electric shock without the chance to escape developed specific behavioral impairments not seen in beagles who did have the chance to escape. Beagles previously exposed to inescapable shock would sit passively and not attempt to escape when they were subsequently shocked in circumstances where there was a chance to escape. This behavior was termed "learned helplessness," and with the extension of studies to the rat, there originated an extensive area of research on the neurochemical and behavioral consequences of uncontrollable stress (Seligman & Beagley, 1975). Originally considered as an animal model for depression, inescapable stress has proven to be a useful model for the study of reactions to traumatic stress (Telner & Singhal, 1984).

Inescapable stress results in the acquisition of specific behaviors and the alteration of multiple brain systems. In rats, stressors such as an electric shock to the foot which they cannot avoid, or being forced to swim in cold water without being able to remove themselves, produce a massive output of norepinephrine, dopamine, and opiates in specific parts of the brain, together with alterations in cortisol, hypothalamic-pituitary-adrenal axis (HPA), and benzodiazepine brain systems. Inescapable stress is associated with impairments in learning and memory manifested by deficits in maze escape behaviors. These deficits appear to be related to alterations in brain structures involved in memory, including temporal lobe, amygdala, and hippocampus (Squire & Zola-Morgan, 1991). Inescapable stress is also associated with conditioned fear or the development of fear responses following exposure to the source of trauma (Davis, 1986). A clinical example of conditioned fear would be the anxiety and fear invoked in a rape victim upon returning to the site of the rape. These changes may persist for extended periods beyond the initial stress, resulting in long-term behavioral disturbances and an inability to respond adequately to subsequent stressors.

Early studies of the neurobiological consequences of inescapable stress focused on noradrenergic brain systems. The locus coeruleus, located in the pons, is the site of 70% of the noradrenergic neurons in the brain. The locus has projections to brain structures involved in learning and memory, including the temporal lobe, hippocampus, hypothalamus, amygdala, nucleus accumbens, and prefrontal cortex (Redmond, 1979). Considering the prominent role of memory in PTSD, it is of interest that brain structures involved in memory are primarily involved in the neurobiological response to inescapable stress. Rats exposed to inescapable stress in the form of electric shock develop learned helplessness behaviors and increased turnover of brain norepinephrine with a relative depletion of norepinephrine in comparison to rats exposed to escapable shocks (Weiss et al., 1970). Inescapable stress is associated with increased release of norepinephrine in the hypothalamus (Yokoo et al., 1990), locus coeruleus, and other brain areas (Anisman & Zacharko, 1985). Repeated exposure to inescapable stress is associated with an eventual depletion of norepinephrine in the hypothalamus and hippocampus (Anisman & Zacharko, 1986; Weiss et al., 1981).

Interventions at the level of noradrenergic brain systems prevent the acquisition of learned helplessness in response to inescapable stress. Prevention of the depletion of norepinephrine by preadministration of the alpha-2 noradrenergic receptor agonist clonidine blocks the development of learned helplessness following exposure to inescapable stress (Anisman et al., 1980). Release of norepinephrine from the locus coeruleus and amygdala following exposure to uncontrollable stress is also attenuated with preadministration of ethanol (Shirao et al., 1988) and benzodiazepines (Drugan et al., 1984), providing a rational explanation for the preference of PTSD patients for these substances.

Noradrenergic brain systems play a role in fear response and alarm states. Increases in heart rate, blood pressure, and alerting behaviors, also essential for the response to life-threatening situations,

are mediated by noradrenergic brain systems. Activation of single-unit noradrenergic neurons in the locus coeruleus of freely moving cats occurs with exposure to stressful stimuli, whereas behaviorally activating but non-stressful stimuli, such as seeing a mouse, do not result in activation of the neurons (Abercrombie & Jacobs, 1987). These studies suggest a role for noradrenergic brain systems in the maintenance of hyperarousal symptoms in patients with PTSD.

Dopaminergic brain systems are also involved in the neurobiological response to inescapable stress. Daily administration of inescapable foot shocks to rats results in increased levels of the dopamine metabolites DOPAC, in the prefrontal cortex, and HVA, in the nucleus accumbens (Kalivas & Duffy, 1989). Excessive dopamine levels in mesolimbic areas could be used to explain psychotic-like symptoms in patients with PTSD. Preadministration of the dopamine agonist apomorphine to rats prevents the acquisition of deficits in learning maze escape behaviors associated with exposure to inescapable stress (Anisman et al., 1980). In addition, rats exposed to inescapable stress develop alterations in the nucleus accumbens, a dopamine-rich area of the brain involved in self-reward systems, resulting in a decrease in pleasure-inducing electrical self-stimulation (Zacharko et al., 1984).

The preference of PTSD patients for benzodiazepines is well known to clinicians familiar with this patient population. The question of why these patients prefer benzodiazepines has potential relevance in understanding the neurobiology of trauma. Benzodiazepine brain systems have been suggested as forming the neurobiological basis of the behaviors and experiences associated with the anxiety response (Guidotti et al., 1990). Inescapable stress results in long-term alterations in benzodiazepine systems. Beta-carboline-3-carboxylic acid (beta-CCE) binds to the benzodiazepine receptor and has partial antagonist properties, which suggests that it may block the effects of benzodiazepines in the brain. Administration of beta-CCE to the rhesus monkey results in behavioral effects consistent with anxiety including struggling, body turning, scratching, defecation, and urination, as well as increases in heart rate and blood pressure (Ninan et al., 1982). Rats exposed to stress in the form of being repeatedly forced to swim in cold water develop decreased binding to benzodiazepine receptors by the benzodiazepine receptor agonist RO-15-1788 in hippocampus, cortex, hypothalamus, and striatum, but not in cerebellum or pons (Weizman et al., 1989; Medina et al., 1983). Stress-induced alterations in benzodiazepine receptor function appear to be mediated by the chloride-ionophore component of the GABA-benzodiazepine receptor complex (Havoundjian et al., 1986). In addition, preadministration of benzodiazepines blocks the sequelae of exposure to inescapable stress in rats, including analgesia to pain, deficits in learning and memory manifested by deficits in shuttle escape behaviors (Drugan et al., 1984), and increased turnover of norepinephrine in the hypothalamus, amygdala, hippocampus, cortex, and locus coeruleus (Ida et al., 1985). These findings provide a rationale for the therapeutic administration of benzodiazepines to patients on the battlefield with acute combat stress reactions.

Endogenous opiate systems are also involved in the stress response. Rats exposed to inescapable stress develop an analgesia to pain known as stress-induced analgesia which can be blocked by administration of the opiate receptor antagonist naltrexone (Maier et al., 1981). Rats exposed to inescapable stress also develop decreased binding of the mu-opiate receptor agonist DAGO in the midbrain, supporting the hypothesis that inescapable stress results in long-term changes in endogenous opiate systems (Stuckey et al., 1989). In addition, preadministration of morphine to rats exposed to inescapable stress attenuates the stress-induced release of norepinephrine in hypothalamus, hippocampus, amygdala, midbrain, and thalamus (Tanaka et al., 1983). Opiates cause a decrease in firing from the locus coeruleus; this provides an explanation for the favorable response of hyperarousal symptoms of PTSD to opiates such as heroin.

Recent studies suggest a relationship between the cortisol response to stress and alterations in brain systems involved in memory. Experiments involving lesions of the hippocampus and adjacent perirhinal, entorhinal, and parahippocampal cortices in monkeys have shown these brain structures to be involved in new learning and memory (Squire & Zola-Morgan, 1991; Zola-Morgan & Squire, 1990). Vervet monkeys who were exposed to sustained stress and died spontaneously were found to have degeneration of neurons specific to the hippocampus (Uno et al., 1989). Cortisol, which is released in response to stress, was later found to have neurotoxic effects associated with memory deficits when implanted in the hippocampus of monkeys (Sapolsky et al., 1990). These memory deficits parallel those seen in PTSD patients, such as amnestic episodes or the forgetting of information such as appointments.

Other studies suggest a relationship between alterations in brain systems involved in the stress response and memory. Conditioned fear is an additional behavioral response associated with exposure to inescapable stress which appears to be mediated by the amygdala in the rat. Clinically, conditioned fear manifests itself as anxiety and fear responses to reminders of the original trauma. Conditioned fear in the rat is associated with an increase in the amplitude of the acoustic startle reflex (Davis et al., 1986) and an increased release of norepinephrine from the hypothalamus (Yokoo et al., 1990). Similarly, PTSD patients exhibit exaggerated startle responses which appear to be magnified by reminders of the original trauma. Fear-potentiated startle is attenuated by drugs that reduce fear or anxiety, such as benzodiazepines and opiates (Davis et al., 1986). Administration of norepinephrine enhances neuronal firing in the hippocampus, suggesting that the norepinephrine released with stress may have an enhancing effect on memory acquisition (Madison & Nicoll, 1982). One can imagine why recollections of traumatic experiences become strongly engraved in memory when there are high levels of circulating norepinephrine. Memory

acquisition is also enhanced by administration of epinephrine and opiate antagonists (McGaugh, 1989).

Clinicians will notice parallels between the behavioral and biological sequelae of inescapable stress and the phenomenology of PTSD symptoms in their patients. The animal model of inescapable stress parallels the experience of being pinned down in combat or being the victim of repeated assaults. Inescapable stress produces a variety of behaviors in animals including abnormal alarm states, aggression, sensitivity to stress, altered sleep patterns, deficits in learning and memory, and withdrawal. These behaviors resemble those seen in patients with PTSD. As reviewed above, there are also a variety of neurobiological alterations produced by exposure to inescapable stress. This may provide a framework in which to conduct investigations designed to determine if similar changes occur in PTSD. For instance, evidence from animal findings of alterations in noradrenergic brain systems is consistent with emerging findings of abnormalities in noradrenergic systems in patients with PTSD as evidenced by abnormal responses to the alpha-2 noradrenergic receptor antagonist yohimbine. The identification of specific neurobiological abnormalities may lead to the development of new psychopharmacological and psychotherapeutic treatments based on the pathophysiology of PTSD.

SELECTED ABSTRACTS

ABERCROMBIE, E.D. & JACOBS, B.L. (1987). **Single-unit response of noradrenergic neurons in the locus coeruleus of freely moving cats. I. Acutely presented stressful and nonstressful stimuli.** *Journal of Neuroscience, 7,* 2837-2843. The present experiment was designed to explore the stress-relatedness of activity in noradrenergic neurons of the locus coeruleus (LC) of behaving cats. A stressor was defined as a stimulus that elicited a significant sympathoadrenal activation as measured by plasma norepinephrine level and heart rate. According to this definition, exposure to 15 min of 100 dB white noise or 15 min of restraint was stressful in cats. In contrast, exposure to inaccessible rats for 15 min was behaviorally activating but nonstressful. The single-unit activity of noradrenergic neurons in the LC of behaving cats was examined under these conditions. The stressful stimuli elicited a significant increase in LC neuronal activity for the entire 15 min stressor duration, whereas the behaviorally activating but nonstressful stimulus elicited no significant change in the activity of these neurons. These results provide evidence that behavioral activation per se is not sufficient to evoke a tonic activation of these neurons. Rather, these data support the hypothesis that the LC is involved in the CNS response to stress and provide additional evidence that the activity of LC noradrenergic neurons increases in association with sympathoadrenal activation.

ANISMAN, H., SUISSA, A. & SKLAR, L.S. (1980). **Escape deficits induced by uncontrollable stress: antagonism by dopamine and norepinephrine agonists.** *Behavioral and Neural Biology, 28,* 34-47. Exposure to inescapable shock was found to retard escape performance of Swiss-Webster mice tested 24 hr later in a modified shuttle task. In accordance with the view that depletion of norepinephrine and dopamine contribute to this effect, the dopamine receptor agonist, apomorphine, and the norepinephrine receptor agonist, clonidine, antagonized the performance disruption. This was the case regardless of whether the drugs were administered prior to inescapable shock or prior to test. These drug effects could neither be attributed to state-dependent effects nor to residual drug action. The data support the contention that the disruption of escape behavior after inescapable shock is due to deficits of response maintenance mediated by dopamine and norepinephrine depletion, rather than to learned helplessness.

DAVIS, M. (1986). **Pharmacological and anatomical analysis of fear conditioning using the fear-potentiated startle paradigm.** *Behavioral Neuroscience, 100,* 814-824. Pharmacological and anatomical analysis of fear conditioning using the fear-potentiated startle paradigm are reviewed. This test measures conditioned fear by an increase in the amplitude of a simple reflex (the acoustic startle reflex) in the presence of a cue previously paired with a shock. This paradigm offers a number of advantages as an alternative to most animal tests of fear or anxiety because it involves no operant and is reflected by an enhancement rather than a suppression of ongoing behavior. Fear-potentiated startle is selectively decreased by drugs such as diazepam, morphine, and buspirone that reduce fear or anxiety clinically. Electrical stimulation techniques suggest that a visual conditioned stimulus ultimately alters acoustic startle at a specific point along the acoustic startle pathway. Relevant visual structures implicated in potentiated startle include the lateral geniculate nucleus, visual cortex, and deep and intermediate layers of the superior colliculus. The central nucleus of the amygdala and the caudal branch of the ventral amygdalofugal pathway projecting to or through the substantia nigra are also necessary for potentiated startle to occur. Electrical stimulation of the central nucleus of the amygdala markedly increases acoustic startle. By combining these behavioral, anatomical, physiological, and pharmacological approaches, it should soon be possible to determine each neural pathway that is required for a stimulus signaling fear to alter startle behavior. Once the exact structures are delineated, it should be possible to determine the neurotransmitters that are released during a state of fear and how this chemical information is relayed along these pathways so as to affect behavior.

IDA, Y., TANAKA, M., TSUDA, A., TSUJIMARU, S. & NAGASAKI, N. (1985). **Attenuating effect of diazepam on stress-induced increases in noradrenaline turnover in specific brain regions of rats: antagonism by Ro 15-1788.** *Life Sciences, 37,* 2491-2498. One-hour immobilization stress increased levels of the major metabolite of brain noradrenaline (NA), 3-methoxy-4-hydroxyphenyl-ethyleneglycol sulfate (MHPG-SO_4), in nine brain regions of rats. Diazepam at 5 mg/kg attenuated the stress-induced increases in MHPG-SO_4 levels in the hypothalamus, amygdala, hippocampus, cerebral cortex, and locus coeruleus (LC) region, but not in the thalamus, pons plus medulla oblon-

gata excluding the LC region, and basal ganglia. The attenuating effects of the drug on stress-induced increases in metabolite levels in the above regions were completely antagonized by pretreatment with Ro 15-1788 at 5 or 10 mg/kg, a potent and specific benzodiazepine (BDZ) receptor antagonist. When given alone, Ro 15-1788 did not affect the increases in MHPG-SO_4 levels. Behavioral changes observed during immobilization stress, such as vocalization and defecation, were also attenuated by diazepam at 5 mg/kg and this action of diazepam was antagonized by Ro 15-1788 at 10 mg/kg, which by itself had no effects on these behavioral measurements. These findings suggest: (1) that diazepam acts via BDZ receptors to attenuate stress-induced increases in NA turnover selectively in the hypothalamus, amygdala, hippocampus, cerebral cortex, and LC region and (2) that this decreased noradrenergic activity might be closely related to relief of distress-evoked hyperemotionality, i.e., fear and/or anxiety in animals.

KALIVAS, P.W. & DUFFY, P. (1989). **Similar effects of daily cocaine and stress on mesocorticolimbic dopamine neurotransmission in the rat.** *Biological Psychiatry, 25,* 913-928. Daily exposure to cocaine or stress has been shown to enhance the motor stimulant effect of a subsequent injection of acute cocaine. Considering that both cocaine and stress enhance dopamine neurotransmission in the central nervous system, it was of interest to determine the effects of daily cocaine and stress on the capacity of acute stress to alter dopamine neurotransmission. Rats were injected with cocaine (15 mg/kg, ip) for 3 days or exposed to daily 20 min of footshock stress (0.3 mA/200 msec/sec) for 10 days. Ten to 14 days later, the rats were exposed to acute footshock or sham shock for 0, 5, 10, or 20 min, and the concentration of dopamine and its metabolites was measured in the A10 and A9 dopamine regions, nucleus accumbens, striatum, and prefrontal cortex. It was found that the daily treatments resulted in an enhancement of dopamine metabolism in the prefrontal cortex and nucleus accumbens in response to acute footshock. In contrast, dopamine metabolism was diminished in the A10 region, and no change was measured in the striatum or A9 region. It is proposed that pretreatment with cocaine or stress alters the response of the mesocorticolimbic dopamine neurons to subsequent stress, so that axonal dopamine neurotransmission is enhanced in the terminal fields and somatodendritic dopamine neurotransmission is diminished. Furthermore, the long-lasting influence of daily cocaine and stress on mesocorticolimbic dopamine responsiveness to subsequent stressful experiences may be relevant in the etiology of psychostimulant-induced psychosis.

MAIER, S.F., DAVIES, S., GRAU, J.W., JACKSON, R.L., MORRISON, D.H., MOYE, T., MADDEN, J. & BARCHAS, J.D. (1981). **Opiate antagonists and long-term analgesic reaction induced by inescapable shock in rats.** *Journal of Comparative and Physiological Psychology, 94,* 1172-1183. Five experiments examined the influence of opiate antagonists on both the short-term analgesic reaction resulting 30 min after exposure to inescapable shock and the long-term analgesic reaction resulting after reexposure to shock 24 hr after inescapable shock exposure. Experiment 1 showed that the long-term analgesic reaction could be reduced by administration of naltrexone prior to exposure to inescapable tail shock. Experiment 2 showed that the reduction in the long-term analgesic reaction produced by naltrexone was dose-dependent. Experiment 3 showed that the long-term analgesic reaction could also be reduced by administration of naltrexone prior to reexposure to shock. Experiment 4 showed that the long-term analgesic reaction could be reduced by administration of a large dose of naloxone prior to reexposure to shock. Experiment 5 showed that the short-term analgesic reaction was reduced by naltrexone administered prior to inescapable shock. Some implications of these results for the biochemical substrates of both learned helplessness and stress-induced analgesia are discussed.

MCGAUGH, J.L. (1989). **Involvement of hormonal and neuromodulatory systems in the regulation of memory storage: Endogenous modulation of memory storage.** *Annual Review of Neuroscience, 12,* 255-287**.** Lasting memory is not formed at the moment that new information is acquired. It is well known that retention can be markedly influenced by treatments administered shortly after learning. Such findings have generally been interpreted as indicating that the treatments affect retention by altering posttraining neural processes underlying the storage of newly acquired information. The hypothesis that memory traces become consolidated over time was originally proposed by Mueller & Pilzecker in 1900. Hebb's 1949 dual-trace hypothesis of memory, which proposed that lasting memory traces are produced by the activity of temporary or short-term memory traces, provided a more explicit view of a possible basis of consolidation. Studies investigating the consolidation of lasting memory traces have focused to a large degree on conditions that disrupt retention. It is clear that retrograde amnesia can be produced by a variety of experimental treatments administered posttraining. More importantly, susceptibility to retrograde amnesia has been conserved in evolution. Evidence that posttraining treatments alter retention in a retrograde fashion has been obtained in studies with humans, monkeys, cats, rodents, birds, fish, and insects.

NINAN, P.T., INSEL, T.M., COHEN, R.M., COOK, J.M., SKOLNICK, P. & PAUL, S.M. (1982). **Benzodiazepine receptor-mediated experimental "anxiety" in primates.** *Science, 218,* 1332-1334. The ethyl ester of ß-carboline-3-carboxylic acid has a high affinity for benzodiazepine receptors in the brain. In the rhesus monkey this substance produces an acute behavioral syndrome characterized by dramatic elevations in heart rate, blood pressure, plasma cortisol, and catecholamines. The effects are blocked by benzodiazepines and the specific benzodiazepine receptor antagonist Ro 15-1788. The benzodiazepine receptor may consist of several subsites or functional domains that independently recognize agonists, antagonists, or "active" antagonists such as ß-carboline-3-carboxylic acid ethyl ester. The results suggest that the benzodiazepine receptor is involved in both the affective and physiological manifestations of anxiety, and that the administration of ß-carboline-3-carboxylic acid ethyl ester to monkeys may provide a reliable and reproducible animal model of human anxiety.

SAPOLSKY, R.M., UNO, H., REBERT, C.S. & FINCH, C.E. (1990). **Hippocampal damage associated with prolonged glucocorticoid exposure in primates.** *Journal of Neuroscience, 10,* 2897-2902. In the laboratory rat and guinea pig, glucocorticoids (GCs), the adrenal steroids that are secreted during stress, can damage the hippocampus and exacerbate the hippocampal damage induced by various neurological insults. An open question is whether GCs have similar deleterious effects in the primate hippocampus. In fact, we showed that sustained and fatal stress was associated with preferential hippocampal damage in the vervet monkey; however, it was not possible to determine whether the excessive GC secretion that accompanied such stress was the damaging agent. The present study examines this possibility.

Pellets of cortisol (the principal GC of primates) were stereotaxically implanted into hippocampi of 4 vervet monkeys; contralateral hippocampi were implanted with cholesterol pellets as a control. One year later at postmortem, preferential damage occurred in the cortisol-implanted side. In the cholesterol side, mild cell layer irregularity was noted in 2 of 4 cases. By contrast in the cortisol-exposed hippocampi, all cases had at least 2 of the following neuropathologic markers: cell layer irregularity, dendritic atrophy, soma shrinkage and condensation, or nuclear pyknosis. Damage was severe in some cases, and was restricted to the CA3/CA2 cellfield. This anatomical distribution of damage, and the cellular features of the damage agree with that observed in instances of GC-induced toxicity in the rodent hippocampus, and of stress-induced toxicity in the primate hippocampus. These observations suggest that sustained GC exposure (whether due to stress, Cushing's syndrome, or exogenous administration) might damage the human hippocampus.

SELIGMAN, M.E.P. & BEAGLEY, G. (1975). **Learned helplessness in the rat.** *Journal of Comparative and Physiological Psychology, 88,* 534-541. Four experiments attempted to produce behavior in the rat parallel to the behavior characteristic of learned helplessness in the dog. When rats received escapable, inescapable, or no shock and were later tested in jump-up escape, both inescapable and no-shock controls failed to escape. When bar pressing, rather than jumping up, was used as the tested escape response, fixed ratio (FR) 3 was interfered with by inescapable shock, but not lesser ratios. With FR-3, the no-shock control escaped well. Interference with escape was shown to be a function of the inescapability of shock and not shock per se: Rats that were "put through" and learned a prior jump-up escape did not become passive, but their yoked, inescapable partners did. Rats, as well as dogs, fail to escape shock as a function of prior inescapability, exhibiting learned helplessness.

SQUIRE, L.R. & ZOLA-MORGAN, S. (1991). **The medial temporal lobe memory system.** *Science, 253,* 1380-1386. Studies of human amnesia and studies of an animal model of human amnesia in the monkey have identified the anatomical components of the brain system for memory in the medial temporal lobe and have illuminated its function. This neural system consists of the hippocampus and adjacent, anatomically related cortex, including entorhinal, perirhinal, and parahippocampal cortices. These structures, presumably by virtue of their widespread and reciprocal connections with neocortex, are essential for establishing long-term memory for facts and events (declarative memory). The medial temporal lobe memory system is needed to bind together the distributed storage sites in neocortex that represent a whole memory. However, the role of this system is only temporary. As time passes after learning, memory stored in neocortex gradually becomes independent of medial temporal lobe structures.

STUCKEY, J., MARRA, S., MINOR, T. & INSEL, T.R. (1989). **Changes in mu opiate receptors following inescapable shock.** *Brain Research, 476,* 167-169. Rats exposed to inescapable shock exhibit profound hypoalgesia. Pharmacological evidence has suggested that changes in endogenous opiate activity may be responsible for the hypoalgesic response. We measured the binding of [^{3}H]DAGO, a selective mu-opiate receptor agonist, in brains of rats exposed to no shock, inescapable shock, or escapable shock. Binding of [^{3}H]DAGO in the midbrains of rats in the inescapable shock group was decreased relative to the other two groups. The decrease in binding appeared to result from a decrease in number of mu-receptors and not a change in affinity. These results support the hypothesis that inescapable shock produces long-term changes in endogenous opiate systems.

TANAKA, M., KOHNO, Y., TSUDA, A., NAKAGAWA, R., IDA, Y., IIMORI, K., HOAKI, Y. & NAGASAKI, N. (1983). **Differential effects of morphine on noradrenaline release in brain regions of stressed and non-stressed rats.** *Brain Research, 275,* 105-115. Effects of morphine on noradrenaline (NA) turnover in the 8 brain regions were investigated in non-stressed and stressed rats. Morphine at 3 mg/kg and 6 mg/kg caused dose-dependent increases in levels of 3-methoxy-4-hydroxyphenylethyleneglycol sulfate (MHPG-SO_4), the major metabolite of brain NA, in the hypothalamus, amygdala, thalamus, hippocampus and midbrain and decreases in NA levels in the first 4 of these regions. In contrast to these enhancing effects of morphine on NA release in non-stressed rats, pretreatment with morphine at 6 mg/kg significantly attenuated immobilization-stress-induced increases in MHPG-SO_4 levels in the above regions. The morphine effects in both states, non-stressed and stressed, were reversed by naloxone at 0.5 mg/kg and 5 mg/kg in the hypothalamus, amygdala and thalamus. These neurochemical changes are apparently related to the distress-evoked hyperemotionality. Behavioral changes observed during the restraint stress such as struggling, vocalization, and defecation were attenuated by morphine at 6 mg/kg and enhanced by naloxone at 5 mg/kg, and this action of morphine was also reversed by naloxone at 5 mg/kg. These results suggest that morphine acts to attenuate stress-induced increases in NA release in the hypothalamus, amygdala and thalamus via opiate receptors, although the drug facilitates NA release in these regions in non-stressed rats. Together with previous findings that naloxone enhances stress-induced increases in NA release selectively in these regions, it is further suggested that endogenous opioids released during stress might act to inhibit NA release in these specific brain areas and that these decreased noradrenergic activities might be closely related to the relief of the distress-evoked hyperemotionality in animals.

UNO, H., TARARA, R., ELSE, J.G., SULEMAN, M.A. & SAPOLSKY, R.M. (1989). **Hippocampal damage associated with prolonged and fatal stress in primates.** *Journal of Neuroscience, 9,* 1705-1711. Sustained exposure to glucocorticoids (GCs), adrenal hormones secreted during stress, can cause neural degeneration in the rat. This is particularly so in the hippocampus, a principal neural target site for GCs, in which GCs can exacerbate the rate of neuron death during normal aging, as well as the severity of neuronal damage after various neurological insults. Thus, stress can be a potent modulator of hippocampal degeneration in the rat. The present report suggests a similar association in the primate. Eight vervet monkeys, housed in a primate center in Kenya, that had died spontaneously from 1984 to 1986, were found at necropsy to have multiple gastric ulcers; a retrospective, neuropathological study was then done of this opportunistic population. Compared with controls euthanized for other research purposes, ulcerated monkeys had marked hippocampal degeneration that was apparent both quantitatively and qualitatively, and both ultrastructurally and on the light-microscopic level. Minimal damage occurred outside the hippocampus. Damage was unlikely to have been due to an agonal or post-mortem artifact. Instead, ulcerated monkeys appear to have been subject to sustained social stress, perhaps in the form of social subordinance in captive breeding groups: most came from social groups, had significantly high incidences of bite wounds at necropsy, and had hyperplastic adrenal cortices, indicative of

sustained GC release. Moreover, the specific hippocampal cell fields damaged in ulcerated animals matched those damaged by GCs in the rodent hippocampus. Thus, this represents the first evidence suggesting that sustained stress, via GC hypersecretion, might be neurodegenerative in the primate.

WEISS, J.M., STONE, E.A. & HARRELL, N. (1970). **Coping behavior and brain norepinephrine levels in rats.** *Journal of Comparative and Physiological Psychology, 72,* 153-160. Avoidance and escape responding affected brain norepinephrine (NE) level. One group of rats avoided or escaped electric shock while "yoked" rats received the same shocks but could not cope. Two avoidance-escape situations were used, one with high avoidance and few shocks and one with mainly escape responding and many shocks. Brain NE was elevated approximately 10% in rats that could avoid or escape shock. Yoked rats that were not able to avoid or escape did not show this elevation. When few shocks were received, yoked animals' levels were not significantly different from controls, but when many shocks were received, their levels were depleted. The results provide evidence for the importance of brain NE in avoidance behavior, and suggest an explanation for avoidance deficits previously attributed to "learned helplessness."

ADDITIONAL CITATIONS
Annotated by the Authors

ANISMAN, H. & ZACHARKO, R.M. (1986). **Behavioral and neurochemical consequences associated with stressors.** *Annals of the New York Academy of Sciences, 467,* 205-229.
Rats were exposed to inescapable stress and escapable stress in the form of foot shock, and brain norepinephrine and dopamine systems were studied. Inescapable stress resulted in an increase in turnover of norepinephrine in the locus coeruleus and other brain areas. Repeated exposure to inescapable stress resulted in the depletion of brain norepinephrine systems in the hypothalamus and hippocampus. Dopamine was decreased in mesolimbic brain structures following inescapable stress. These findings suggest that stress results in depletion of norepinephrine and dopamine in specific brain areas.

DRUGAN, R.C., RYAN, S.M., MINOR, T.R. & MAIER, S.F. (1984). **Librium prevents the analgesia and shuttlebox escape deficit typically observed following inescapable shock.** *Pharmacology, Biochemistry and Behavior, 21,* 749-754.
Rats exposed to inescapable stress develop deficits in memory evidenced by impairments in maze escape behaviors and analgesia. Preadministration of librium prevents the development of analgesia and memory deficits. This suggests that benzodiazepine brain systems may play a role in the development of the behavioral and biological consequences of inescapable stress.

GUIDOTTI, A., BARALDI, M., LEON, A. & COSTA, E. (1980). **Benzodiazepines: A tool to explore the biochemical and neurophysiological basis of anxiety.** *Federation Proceedings, 39,* 1039-1042.
Research on the relationship between benzodiazepine brain systems and anxiety is reviewed and future studies to test the hypothesis that benzodiazepine brain systems are involved in the neurobiology of anxiety are suggested.

HAVOUNDJIAN, H., PAUL, S.M. & SKOLNICK, P. (1986). **Acute, stress-induced changes in the benzodiazepine/gamma-aminobutyric acid receptor complex are confined to the chloride ionophore.** *Journal of Pharmacology and Experimental Therapeutics, 237,* 787-793.
Uncontrollable stress in rats is associated with long-term changes in the GABA-benzodiazepine receptor complex which are located in the chloride ionophore. This indicates that the GABA-benzodiazepine receptor complex may play a role in the neurobiological sequelae of inescapable stress.

MADISON, D.V. & NICOLL, R.A. (1982). **Noradrenaline blocks accommodation of pyramidal cell discharge in the hippocampus.** *Nature, 299,* 636-638.
The effects of norepinephrine applied to hippocampal pyramidal neuron cell cultures was studied. Norepinephrine blocked the calcium-activated potassium conductance in these neurons, resulting in a reduction in the spike frequency adaptation which normally occurs with repeated depolarizations of neurons. This suggests that norepinephrine has a stimulating effect on hippocampal neurons, and possibly, by extension, on memory.

MEDINA, J.H., NOVAS, M.L., WOLFMAN, C.N.V., LEVI DE STEIN, M. & DE ROBERTIS, E. (1983). **Benzodiazepine receptors in rat cerebral cortex and hippocampus undergo rapid and reversible changes after acute stress.** *Neuroscience, 9,* 331-335.
Rats were exposed to forced swimming, and benzodiazepine receptor binding in the cortex and hippocampus was measured. This stress resulted in a 30% decrease in benzodiazepine receptor binding. These results suggest that acute stress is associated with alterations in benzodiazepine brain systems.

SELIGMAN, M.E.P. & MAIER, S.F. (1967). **Failure to escape traumatic shock.** *Journal of Experimental Psychology, 74,* 1-9.
In the first study of inescapable stress, Seligman et al. noted that 66% of beagles exposed to inescapable shocks develop an incapacity to escape subsequent shocks, a behavior not seen in animals exposed to escapable shocks. The authors conclude that inescapable stress is associated with a specific behavioral paradigm they term "learned helplessness."

SHIRAO, I., TSUDA, A., IDA, Y., TSUJIMARU, S., SATOH, H., OGUCHI, M., TANAKA, M. & INANAGA, K. (1988). **Effect of acute ethanol administration on noradrenaline metabolism in brain regions of stressed and nonstressed rats.** *Pharmacology, Biochemistry and Behavior, 30,* 769-773.
The effects of ethanol on noradrenaline (NA) metabolism of brain regions in stressed and nonstressed rats were investigated. In nonstressed rats, ethanol significantly increased MHPG-SO_4 levels in the hypothalamus, hippocampus, and cerebral cortex, but not in the amygdala or in the LC region. In stressed rats, ethanol attenuated stress-induced increases in MHPG-SO_4 levels preferentially in the amygdala and LC region, but not in the remaining three regions. These results suggest that the attenuating effect of ethanol on stress-induced increases in NA turnover in the amygdala and LC region might be related to the stress-relieving properties of this drug.

TELNER, J.I. & SINGHAL, R.L. (1984). **Psychiatric progress: The learned helplessness model of depression.** *Journal of Psychiatric Research, 18,* 207-215.
The authors review the construct of learned helplessness as an animal model for psychiatric disorders with a discussion of the history of research in the area.

WEISS, J.M., GOODMAN, P.A., LOSITO, B.G., CORRIGAN, S., CHARRY, J.M. & BAILEY, W. (1981). **Behavioral depression produced by an uncontrollable stressor: Relationship to norepinephrine, dopamine, and serotonin levels in various regions of rat brain.** *Brain Research Reviews, 3,* 167-205.
Rats were exposed to inescapable footshock and behavioral and neurochemical changes were studied. Decreases in norepinephrine in the hypothalamus, locus coeruleus, and cortex were observed in rats exposed to inescapable, but not escapable, stress. These changes were associated with a behavioral depression. The authors concluded that stress-induced decreases in norepinephrine, especially in the locus coeruleus, are involved in mediating the behavioral depression known as learned helplessness.

WEIZMAN, R., WEIZMAN, A., KOOK, K.A., VOCCI, F., DEUTSCH, S.I. & PAUL, S.M. (1989). **Repeated swim stress alters brain benzodiazepine receptors measured in vivo.** *Journal of Pharmacology and Experimental Therapeutics, 249,* 701-707.
Rats were exposed to repeated stress in the form of swimming in cold water for 7 days and benzodiazepine receptor binding was assessed. Binding of Ro-15-1788 to benzodiazepine receptors was decreased in hippocampus, cortex, hypothalamus, and striatum, but not in the cerebellum or pons. These findings suggest that stress results in a decrease in benzodiazepine receptor binding in specific brain regions.

YOKOO, H., TANAKA, M., YOSHIDA, M., TSUDA, A., TANAKA, T. & MIZOGUCHI, K. (1990). **Direct evidence of conditioned fear-elicited enhancement of noradrenaline release in the rat hypothalamus assessed by intracranial microdialysis.** *Brain Research, 536,* 305-308.
Rats were exposed to inescapable stress in the form of electric footshocks as well as escapable stress. Inescapable stress was associated with increased release of norepinephrine from the hypothalamus. Reexposure to the stressful environment (conditioned fear), without footshock, resulted in increased release of norepinephrine as well.

ZACHARKO, R.M., BOWERS, W.J., KELLEY, M.S. & ANISMAN, H. (1984). **Prevention of stressor-induced disturbances of self-stimulation by desmethylimipramine.** *Brain Research, 321,* 175-179.
Rats were exposed to inescapable shock, and self-stimulation with electrical activity to the nucleus accumbens, a brain region which may play a role in pleasure, was measured. Rats exposed to inescapable, but not escapable, stress developed a reduction in desmethylimipramine. These findings suggest that inescapable stress may have an effect on a pleasure system of the brain, the nucleus accumbens.

ZOLA-MORGAN, S.M. & SQUIRE, L.R. (1990). **The primate hippocampal formation: Evidence for a time-limited role in memory storage.** *Science, 250,* 288-290.
The ability of monkeys to discriminate pairs of objects after removal of the hippocampus was compared to monkeys without removal of the hippocampus. Monkeys without the hippocampus exhibited severe deficits in ability to remember recently learned objects, although they were able to remember objects learned long ago. These results suggest that the hippocampal formation is required for only a short time after learning.

PILOTS Update

The PILOTS database has now grown to over 3,000 records. We still have a considerable backlog of older papers to evaluate, index, and enter into the database, and we are receiving new publications at an alarming rate. We hope to double our indexing staff during the next few months; the addition of this new person will enable us to keep up with the new literature, and to expand our efforts at locating and indexing important older papers. Our goal is to make PILOTS a one-stop source for references to papers on traumatic stress. We haven't reached that goal yet, but we have got to the point where any search of the PTSD literature is seriously incomplete unless it includes PILOTS.

Searching any database is frustratingly inefficient without good documentation. For that reason, one of our high priorities has been the preparation of a PILOTS User's Guide, and we are pleased to announce its availability. The first edition is written for experienced searchers of online bibliographical databases. It gives instructions for accessing and searching PILOTS both on floppy disk using ProCite and as the PTSD subfile of the Combined Health Information Database (CHID) on BRS. A second edition, which we hope to make available during the early spring of 1992, will be written for mental health clinicians and researchers as well as for information professionals. It will include a discussion of database selection, search strategy formulation, and evaluation of search results, as well as illustrations of PILOTS search sessions.

A copy of the first edition of the PILOTS User's Guide will be sent to each VA medical library. It will also be available for purchase from the National Technical Information Service. The NTIS order number is PB92-100252; the cost in the United States is $19.00 plus a $3.00 handling fee per order. To order the PILOTS User's Guide, or to determine the price to customers outside the United States, write to: National Technical Information Service, Springfield, Virginia 22161. Telephone orders are accepted at (703) 487-4650. Please note that the National Center for PTSD is unable to fulfill requests for the PILOTS User's Guide.

We are currently conducting a survey of potential PILOTS users, with the help of marketing students at Dartmouth College's Tuck School of Business. We shall use the results of this study to help us make the PILOTS database more readily available and more responsive to the needs of the traumatic stress community.

PTSD RESEARCH ACTIVITIES AT THE SAN FRANCISCO VA MEDICAL CENTER

Charles R. Marmar, MD and Daniel S. Weiss, PhD

In 1979 we began collaborating with a group of investigators at the University of California, San Francisco Medical School focused on the understanding and treatment of the reactions to traumatic stress in civilians. This original group, assembled by Mardi Horowitz, MD, as the Center for the Study of Neuroses, concentrated on traumatic bereavement as well as accidents, assaults, and other civilian traumas. That near-decade-long collaboration produced theoretical models for differentiating normal from pathological stress response, a validated model for time-limited dynamic psychotherapy of traumatic stress reactions, construction and validation of measures of stress response and outcome, and empirical studies of both the relationship of the treatment process to treatment outcome and the descriptive phenomenology and intrapsychic transformations of those who had been traumatized in a variety of ways.

In 1986 we left the Center for the Study of Neuroses to join the National Vietnam Veterans Readjustment Study as Co-Principal Investigators. This began a still-ongoing collaboration with the other NVVRS Co-PIs: Richard Kulka, PhD, William Schlenger, PhD, John Fairbank, PhD, Richard Hough, PhD, and B. Kathleen Jordan, PhD. The initial findings of the NVVRS were nationally representative estimates of the high prevalence and co-morbidity of combat-related PTSD in Vietnam theater veterans, surprisingly low utilization of both non-VA and VA mental health services, differentially higher rates of PTSD for minority males, the clear impact of exposure to war zone stressors on the prevalence of PTSD, and the profound impact on families of veterans with PTSD. Intensive analyses of the NVVRS data are ongoing, with emphasis on the role of predisposing factors, the relationship of trauma and dissociation, the interrelationship of PTSD symptoms, and a large number of explorations of psychometric issues in the assessment of PTSD and co-morbid disorders.

At the conclusion of the VA's contract with the NVVRS study team in 1989, we affiliated with the San Francisco VA Medical Center and over the past three years have established a PTSD Program. The clinical activities comprise a Post-Traumatic Stress Disorder Clinical Team (PCT), an evaluation and brief treatment PTSD Inpatient Unit (EBTPU), and most recently a Substance Use Post-Traumatic Stress Disorder Team (SUPT). The teaching activities include training of psychiatric residents, psychology interns and externs, medical students, and pre-doctoral and post-doctoral fellows.

The research activities of the San Francisco VAMC PTSD Program involve both veteran and non-veteran populations. With our veterans, we are actively involved in both the further elucidation of the phenomenology and natural history of traumatic stress and PTSD, as well as co-morbid disorders. We have Merit Review funding to investigate these issues as well in the NVVRS sample. Our other main focus in our veteran population is on treatment development and assessment of group therapy, family therapy, pharmacotherapy, and challenge exercise adjuncts. Collaborating with us in these efforts are Keith Armstrong, LCSW, Westley Clark, MD, Hsiao-ti Falcone, PhD, Nick Kanas, MD, Paul Koller, PhD, Patricia Lund, PhD, Stephen Pennington, PhD, Rose Sandecki, RN, Frank Schoenfeld, MD, Victoria Tichenor, PhD, Laurie Townsend, MSW, and Sally Vrana, MD.

We are funded by the National Institute of Mental Health to conduct a longitudinal study of the impact on rescue workers of working on the Cypress structure freeway collapse resulting from the October 1989 Loma Prieta Earthquake. The study aims to contribute to the understanding of the course, complications, risk factors, psychophysiology, and psychological mechanisms mediating responses to extreme stress exposure in the face of natural disaster.

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