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In Vivo Serotonin Release and Learned Helplessness

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Abstract. Learned helplessness, a behavioral depression caused by exposure to inescapable stress, is considered to be an animal model of human depressive disorder. Like human depression, learned helplessness has been associated with a defect in serotonergic function, but the nature of this relationship is not entirely clear. We have used in vivo microdialysis brain perfusion to measure serotonin (5-hydroxytryptamine, 5HT) in extracellular space of medial frontal cortex in conscious, freely moving rats. Basal 5HT levels in rats perfused before exposure to tail-shock stress did not themselves correlate with subsequent learned helplessness behavior. However, 5HT release after stress showed a significant increase with helpless behavior. These data support the hypothesis that a cortical serotonergic excess is causally related to the development of learned helplessness.

Key Words. Depression, animal model, 5-hydroxytryptamine, cortex, brain microdialysis, rats.

Serotonin (5-hydroxytryptamine, 5HT) is thought to play a role in the pathophysiology of depression. Generally, a 5HT deficit is presumed to correlate with the development of depressive symptoms. Perhaps the best evidence supporting this view is the report that dietary depletion of tryptophan, the 5HT precursor, causes the reemergence of acute depressive symptoms in treated, recovered patients (Delgado et al., 1990). Other supporting evidence derives from the finding that specific serotonergic reuptake blockers such as fluoxetine are effective antidepressants. However, not all evidence relating 5HT to depression is positive. Notably, the 5HT precursors tryptophan (TRP) and 5-hydroxytryptophan (5HTP) have not been shown to be consistently effective in treating depression (Curzon, 1988).

Learned helplessness is a stress-induced behavioral depression with enough similarities to human depression to warrant its consideration as an animal model of this illness (McKinney and Bunney, 1969). Helpless rats show behavioral passivity, appetite and sleep disturbance, and decreased motor function. These deficits can be reversed by chronic treatment with antidepressants and electroconvulsive shock (Sherman et al., 1982). Serotonin's involvement in learned helplessness has been

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studied by several investigators, but without the development of a clear and consistent pattern of correlation between biochemistry and behavior.

A 5HT deficit in learned helplessness is suggested by the decreased release of 5HT from cortical and septal tissue slices of rats with learned helplessness. Serotonin release was elevated in naive rats receiving chronic imipramine (IMI), and the 5HT deficit in rats with learned helplessness was normalized by chronic IMI (Sherman and Petty, 1982). The injection of 5HT into frontal cortex also reversed helpless behavior (Sherman and Petty, 1980), and a specific 5HT reuptake blocker, alaproclate, reversed learned helplessness (Plaznik et al., 1988). Learned helplessness reversal was also noted with other 5HT uptake blockers, but only at intermediate doses (P. Martin et al., 1990). Naive animals treated with the 5HT receptor blocker methysergide exhibited behavioral learned helplessness, and the behavioral deficit was reversed by the 5HT releasing agent, *p*-chloroamphetamine (Hamilton et al., 1986). Enhancement of learned helplessness with calcium also led to a concurrent decrease in brain 5HT turnover (Trulson et al., 1986). Finally, the $5HT_{1A}$ agonists ipsapirone and buspirone have been shown to reverse learned helplessness (Drugan et al., 1987; Graeff et al., 1989).

Other investigations suggest that a 5HT excess accompanies learned helplessness. The 5HT precursors TRP and 5HTP, when given intraperitoneally in doses sufficient to raise brain 5HT levels, caused a learned helplessness-like behavior in naive rats that was blocked by methysergide (Brown et al., 1982). Brown et al. (1982) also found methysergide prevented the development of stress-induced learned helplessness. Elevated levels of 5HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) were found in frontal neocortex, hippocampus, and hypothalamus of rats subjected to inescapable stress, and depletion of 5HT with *p*-chlorophenylalanine (PCPA) protected rats from development of learned helplessness after stress (Edwards et al., 1986). Recently, J.V. Martin et al. (1990) replicated the findings of elevated tissue levels of 5HT in rats with learned helplessness, but they were unable to show compensatory changes in $5HT_2$ receptors.

Other studies report ambiguous or inconclusive results. Edwards et al. (1991) found the change in density of the 5HT uptake site to depend on the particular brain region studied in both stressed and spontaneously helpless rats. Anisman et al. (1979) found neither PCPA nor 5HTP to have any effect on stress-induced behavioral depression, while Plaznik et al. (1988) reported paradoxical effects with 5HT depletion. Soubrie et al. (1986) reported that lesions sufficient to produce a 70% loss of tryptophan hydroxylase activity altered neither learned helplessness nor the ability of antidepressants to reverse it. High doses of 5HT uptake inhibitors were without effect on learned helplessness (P. Martin et al., 1990). We have recently shown (Petty and Kramer, 1987) that in vivo microdialysis levels of 5-HIAA in frontal cortex were similar in inescapably stressed and control rats, but rats that had escapable stress had significantly higher levels, indicating possibly a higher 5HT turnover or metabolism rate in rats receiving escapable shock. We have also shown with this in vivo technique that three different treatments preventing learned helplessness—acute diazepam, chronic imipramine, or behavioral training—all share a common neurochemical effect in preventing depletion of intracellular stores of 5HT as they prevent behavioral depression (Petty et al., 1992).

Brain microdialysis perfusion provides for direct, real-time measurement of neurochemical concentrations in extracellular space in conscious, freely moving animals. This technique provides a close approximation to synaptic neurotransmitter release. In the present work, we have used microdialysis to study release of 5HT in frontal cortex of rats before and after inescapable tail-shock stress, and correlated these levels with behavioral measures of learned helplessness.

Although several brain regions and neurotransmitters are implicated in the development and maintenance of learned helplessness in our theoretical model, the model suggests that 5HT in frontal neocortex may play a unique role in mediating reversal of learned helplessness (Sherman and Petty, 1982). Whether cortical 5HT also mediates the development of learned helplessness or its prevention was the focus of the present investigation.

Methods

Animals. Subjects were male rats (Wistar) weighing 250-300 g at the time of experimentation. Rats were housed in groups of six with ad libitum access to chow and water, and a 12-hour light/dark cycle. All subjects were given 2 weeks' adaptation in the animal facility before experimentation. The experimental protocol was approved by the Animal Studies Committee of the University of Texas Southwestern Medical School and the Dallas Department of Veterans Affairs Medical Center, and it complies with the guidelines for treatment of laboratory animals of the National Institutes of Health.

Behavioral Experiment. Inescapable stress was delivered in plastic stress chambers modeled after the design of Weiss et al. (1981) with the manipulandum wheel locked in position. Wire electrodes coated with conductive paste were securely fastened to the rat's tail, which protruded from the chamber and was fastened to a plastic rod. Eighty trials of tail-shock were presented. The first 20 trials began with an unsignaled 5-second, 1-mA scrambled shock that was increased by 0.3 or 0.4 mA every 20 trials to a final current of 2 mA. The intertrial interval had an average of 60 seconds (range 25-180 seconds). These parameters have been shown by Maier et al. (1973) to be the minimal amount of stress required to produce a reliable performance deficit on subsequent testing. Control (no-stress) rats were secured in the plastic stress chambers for 80 minutes similar to stressed rats, but no shock was delivered. All rats were tested for learned helplessness using a two-way shuttlebox (Drugan et al., 1989). Briefly, each trial began with a warning tone followed by a 1-mA floor-grid shock 5 seconds later. The first five trials could be terminated by a single crossing of the shuttlebox (FR1). These FR1 trials were not affected by prior stress, and they served to test only motor function of animals. The subsequent 25 trials required two crossings of the shuttlebox to terminate the shock (FR2). If the required escape response did not occur within 30 seconds of shock onset, the trial was automatically terminated. Both Petty et al. (1992) and Drugan et al. (1989) have shown that with this behavioral protocol, a criterion of 25-second mean latency (trial onset) for the 25 FR2 trials reliably discriminates between helpless and nonhelpless rats. In other words, naive rats with no prior shock exposure routinely (95% confidence interval) score mean latencies < 25 seconds, while about half of rats receiving inescapable tailshock have mean escape latencies ≥ 25 seconds.

Microdialysis. Probes were constructed using the loop design of Zetterstrom et al. (1983) with cellulose dialysis tubing. Probes were implanted under phenobarbital (Nembutal) anesthesia into the frontal neocortex using stereotaxic guidance (coordinates from bregma 4.2 A, 0.5 L, 4.8 V; Pellegrino et al., 1979). One day after surgery, the microdialysis probes were connected to a syringe pump (Harvard Apparatus) through a liquid swivel with the rats in a cylindrical polystyrene chamber (30×60 cm) and perfusion was maintained at 1.8 μl/minute

with Ringer's solution (147 m*M* NaCl, 2.3 m*M* $CaCl_2$, 4.0 m*M* KCl, *p*H 6.0). After a 1-hour washout period, samples were collected every 20 minutes and immediately assayed for 5HT by high performance liquid chromatography (HPLC, see below). The perfusion normally lasted a maximum of 3 hours. Basal levels of 5HT were determined on the last three to four samples. The rats were then disconnected from the perfusion apparatus and given inescapable stress. On the day after the first perfusion, rats were again perfused for another 3-hour experiment and were then tested for the development of learned helplessness.

After behavioral testing for learned helplessness, the probe was injected with cresyl violet dye and the rats were sacrificed by phenobarbital overdose. The brain was removed, fixed in formalin, and then sliced. Probe placement was verified by examination under a dissecting microscope. All animals in which the probe was not in medial frontal cortex were discarded from statistical analysis.

Biochemical Procedure. Microdialysis perfusate was injected immediately after collection into an HPLC system consisting of a pump, coulometric detectors (ESA Inc., Bedford, MA), and recording integrator (Spectra Physics, Houston, TX). Detectors 1 and 2 were set at +0.05 and +0.23 V, respectively. The mobile phase consisted of 0.1 M NaH_2PO_4 (*p*H 3.4), 100 μM EDTA, 50 mg/l sodium heptyl sulfonate, and 5% (v/v) methanol. The mobile phase was pumped through a C-18 column (8 × 0.46 cm) at 1.6 ml/minute. Quantitation of 5HT was achieved with external standards. Sensitivity of this assay was 0.5 pg.

Summary of Procedure. On day 1, rats were implanted with probes; on day 2, they were perfused (prestress basal levels) and then given 80 trials of tail-shock stress or the nonstressed control condition; and on day 3, they were again perfused (poststress basal levels) and tested in the shuttlebox.

Results

For purpose of data analysis, the following three groups were compared: control rats ($n = 4$), stressed and helpless rats ($n = 7$), and stressed and nonhelpless rats ($n = 8$). The stressed rats performed as the control rats did in the FR1 mean (± SD) latency (control rats: 8.8 ± 4.1; helpless rats: 12.6 ± 6.3; nonhelpless rats: 8.6 ± 0.9). The mean (± SD) latencies for FR2 were no different in the nonstressed control rats and the stressed nonhelpless rats (control rats: 11.3 ± 1.9; nonhelpless rats: 13.5 ± 3.6). However, as defined above, the helpless group had higher FR2 mean (±SD) latencies (helpless rats: 29.0 ± 4.9). The three groups did not differ when prestress basal levels of 5-HT were compared (analysis of variance: $F = 0.22$; $df = 2, 16$; $p = 0.80$) (see Table 1). However, the poststress levels of 5HT differed significantly among the three groups (analysis of variance: $F = 3.7$; $df = 2, 16$; $p = 0.05$) with levels decreasing from prestress values in the control and nonhelpless groups. Post hoc contrast testing showed the learned helplessness group was higher than the control group ($F = 4.6$; $df = 1, 16$; $p = 0.05$) and the nonhelpless group ($F = 6.0$; $df = 1, 16$; $p = 0.03$).

Discussion

Levels of 5HT in microdialysis perfusate are in equilibrium with neurotransmitter

Table 1. Basal levels of cortical serotonin in the perfusate before and after tail-shock stress

	Control rats		Nonhelpless rats		Helpless rats	
	Mean	SD	Mean	SD	Mean	SD
Before stress	2.0	1.0	1.9	0.7	1.8	0.2
After stress	1.3	0.6	1.4	0.4	2.1	0.8

Note. Levels are in pg/20 μl.

levels in extracellular space. As expected of a synaptic released substance, 5HT levels in perfusate have been demonstrated to be K^+-stimulated, Ca^{++}-dependent, and decreased by TTX, which blocks neuronal impulse flow. Also, levels of 5HT in perfusate are increased by the specific 5HT reuptake blocker fluoxetine (Petty et al., 1992). Taken together, these data support the conclusion that 5HT measured by microdialysis perfusion is of likely neuronal origin, probably reflecting exocytotic vesicular release.

The present work demonstrates the feasibility of using brain microdialysis perfusion for the in vivo neurochemical study of behavior. Shuttlebox performance of animals with microdialysis probe implants was comparable to that of unoperated control rats in previous experiments (Drugan et al., 1989; Petty et al., 1992). This work confirms recent reports (Adell et al., 1989; Kalen et al., 1989; Schwartz et al., 1990; Petty et al., 1992) on the feasibility and utility of microdialysis perfusion to study the 5HT system concurrently with behavior.

Through the years, investigators have consistently found a range of susceptibility of animals to the development of stress-induced behavioral depression or learned helplessness. Although the precise proportion of animals rendered helpless by stress can vary between 15% (Henn et al., 1986) and 85% (Sherman and Petty, 1980), depending on experimental protocol or strain of rat (Wieland et al., 1986), gender, and perhaps other factors such as handling and season, one thing is clear: no investigator has reported all subjects to become helpless after stress. Finding a neurochemical substrate for this vulnerability to stress is of considerable theoretical interest and has potential clinical utility.

Our data suggest that basal levels of extracellular 5HT in the frontal neocortex of animals before stress do not explain neurochemical vulnerability to stress. However, the change in basal extracellular 5HT levels due to stress did correlate with the development of learned helplessness. That is, rats with a greater increase in basal levels of 5HT caused by inescapable stress were more likely to become helpless than rats with less cortical 5HT increase. These data implicate a *5HT excess* in extracellular space in the development of learned helplessness. A regional neuroanatomy for learned helplessness has been hypothesized (Sherman and Petty, 1982). In this model, serotonin plays a key role in developing and maintaining learned helplessness in frontal neocortex and septum. Most of the data supporting

this model derive from experiments examining 5HT release from tissue slices and from direct microinjection of serotonin into brain regions. Other learned helplessness research supports a role for 5HT in hippocampus and hypothalamus (Edwards et al., 1992). These experiments studied receptor binding and should be viewed as complementary to the other work. Our rationale for studying the prefrontal cortex in the present experiments, which should be regarded as quite preliminary, was simple. Prefrontal cortex was the only brain region in which direct microinjection of tricyclic antidepressant both reversed and prevented learned helplessness (Petty and Sherman, 1979, 1980). Prefrontal cortex was the only brain region (of 12 studied) in which 5HT microinjection reversed learned helplessness and in which it did so 1 hour after injection. Also, our previous work suggests prefrontal cortex to initiate neurochemical changes associated with learned helplessness, since changes in 5HT release in septum follow and depend upon previous changes in prefrontal cortex 5HT activity (Petty and Sherman, 1983).

Extrapolation to human depression is tentative at best. There remains a number of problems in applying the learned helplessness model to human depression. These have been well and recently reviewed (McKinney, 1988; Zacharko and Anisman, 1989) and need not be enumerated here. Suffice it to say, learned helplessness is a stress-induced depression, and we do not fully understand the role of stress in the etiology of human depression. Caveats aside, the 5HT hypothesis of human depression usually assumes a *5HT deficit* to accompany depression. This assumption is made because the biogenic amine depletor reserpine can cause depression, and because some antidepressant drugs block reuptake or metabolism of 5HT. However, some evidence points to a possible 5HT excess in depression. An increase in 5HT in cerebrospinal fluid from depressive patients has been reported (Gjerris et al., 1987), as well as an increase in 5HIAA in brains of depressed suicides (Owen et al., 1986). In fact, the new antidepressant tianeptine decreases serotonergic transmission (Curzon et al., 1992).

A great deal of work remains to be done. For example, what is the time course of the increased basal 5HT release in helpless animals? Does intraneuronal depletion ensue when a long-term behavior defect is observed? Is the correlation between the increase in extracellular 5HT and learned helplessness unique to frontal cortex? Our neurochemical model of learned helplessness (Sherman and Petty, 1982) would predict that it is, but other brain regions must be studied. J.V. Martin et al. (1990) found elevated 5HT levels in hippocampus of rats with learned helplessness.

What is the involvement of other neurotransmitters? Research in progress will examine norepinephrine release in hippocampus, where our model predicts a correlation between basal levels of the neurotransmitter before stress should correlate with vulnerability to learned helplessness. Also, the role of amino acid neurotransmitters, particularly γ-aminobutyric acid (GABA), in both depression and learned helplessness is well documented (Lloyd et al., 1989), and the interactions of GABA and 5HT are known, but not yet studied in the learned helplessness paradigm in vivo. Further work should help clarify the role of 5HT in the development of learned helplessness in vivo, and whether manipulations of 5HT can prevent the development of learned helplessness.

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