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Glutathione as a Cerebral Substrate in Depressive Behavior

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PAL, S. N. AND P. C. DANDIYA. *Glutathione as a cerebral substrate in depressive behavior.* PHARMACOL BIOCHEM BEHAV **48**(4) 845–851, 1994.—Behavioral depression through inescapable foot shock stress in Swiss albino mice was measured on the basis of their performance in an open field test (OFT) and a forced swimming test (FST). Glutathione (GSH) and various antidepressants (imipramine, maprotiline, fluvoxamine, trazodone, and alprazolam) were able to, either fully or partly, prevent and/or reverse the shock-induced behavioral depression. The GSH level was measured in the cerebral cortex, cerebellum, brain stem, and the hypothalamus in shocked mice to ascertain a possible correlation between brain GSH and stress-induced depression, under conditions of preshock and postshock antidepressant treatments as well as in the absence of the drugs. There was an appreciable depletion of cortical GSH in shocked mice that was corrected to varying degrees by the different antidepressants. The results suggest a close link between stress-induced behavioral depression, increased monoaminergic utilization, oxidative stress, and brain GSH.

Inescapable shock Behavioral depression Antidepressant Imipramine Maprotiline Fluvoxamine
Trazodone Alprazolam Glutathione Monoamine oxidase Hydrogen peroxide Oxidative stress

DEPRESSION today is seen as an illness like ulcers or high blood pressure, the result of an interplay of biological and psychological forces. Until now, research has centered around establishing the relationships between depression and biogenic amines, namely, norepinephrine (NE), dopamine (DA), and 5-hydroxytryptamine (5-HT). A fair amount of data has accumulated suggesting a role for γ-aminobutyric acid (GABA) in depression. Though the mechanisms of action of newer antidepressant drugs along with improved techniques like neuroimaging have helped in identifying the involvement of various neurotransmitter receptors in the disease, the last word on the cerebral substrates of depressive behavior is not yet in.

Glutathione (L-γ-glutamyl-L-cysteinyl-glycine; GSH), a tripeptide thiol found in virtually all cells, functions in metabolism, transport, and cellular protection. Blood GSH level has been reported to be in or below the lower normal range in untreated patients with manic-depressive, involutional, or schizophrenic psychoses (2). Different stressors, including cold (30), heat (32), cold restraint (29), etc., can decrease glutathione content in various tissues in animals. Because many animal models of depression (such as depression through inescapable shock, forced swimming, tail suspension, etc.) involve subjecting experimental animals to various forms of stressors, it should be interesting to study changes, if any, in the GSH levels in stressed animals. Such a study could yield valuable information regarding a possible role for GSH in depression. In the present investigation, changes in behavior and brain GSH levels were analyzed in mice subjected to inescapable foot shock stress, an accepted method of inducing behavioral depression in rodents (21,28). Because behavioral depression following an acute uncontrollable stressor might result from 5-HT (7), NE (34), or GABA (19) reductions, the antidepressants imipramine (inhibiting the reuptake of NE and 5-HT), maprotiline (selective for NE reuptake inhibition), fluvoxamine (selective for 5-HT reuptake inhibition and potentiation of NE transmission), and the GABAergic alprazolam were used to study their effects on depressed animals. Glutathione was also administered to study any possible effects the drug might have on depressed behavior. Further, GSH levels were measured in various brain regions in shocked animals in the presence of antidepressants to correlate behavior and brain GSH.

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METHOD

Animals

Adult Swiss albino mice of either sex, weighing 25 ± 5 g, were obtained from the Central Animal Facility of the University of Jamia Hamdard, New Delhi, India. They were housed six to a cage and maintained on a 12 L : 12 D day : night cycle with free access to food and water. Animals were drawn at random for test and control and were tested during the light cycle between 1200–1600 h.

Drugs

Hydrochloride salts of imipramine (16 mg/kg b.wt., S. G. Pharmaceuticals, Bombay, India), maprotiline (16 mg/kg b.wt., Ciba-Geigy, Basel, Switzerland), fluvoxamine (10 mg/kg b.wt., Kali Duphar Pharma, Berne, Switzerland), trazodone (20 mg/kg b.wt. and 10 mg/kg b.wt.), alprazolam (2 mg/kg b.wt.) (both from Sun Pharmaceutical Industries, Bombay, India), and GSH (500 mg/kg b.wt., Sigma Chemical Co., St. Louis, MO) were used. All drug solutions were prepared in distilled water except alprazolam, which was suspended in 0.5% carboxymethylcellulose. All treatments were by the IP route. Imipramine, maprotiline, fluvoxamine, and GSH were administered 30 min (6) and alprazolam 60 min (12) before shock. Trazodone was administered 60 min prior to shock on the basis of detailed pilot experiments conducted to accommodate the strong sedation induced by the drug. In postshock studies, drugs were given just after shock treatment (6). The doses for fluvoxamine and GSH were derived from previous reports (15,18), and the dose for alprazolam was based on pilot experiments carried out with the drug in our laboratory (unpublished data). All other drug doses were computed from absolute human doses using surface area ratio of mouse to man. Because 20 mg/kg of trazodone brought about a significant depletion of mouse brain cortical GSH, 10 mg/kg of the drug was also used to study the effect of a lower dose of trazodone on cortical GSH.

Shock-Induced Depression

The method was based on the procedures outlined by other investigators (6,21,28). Four mice were placed on a grid floor (26 × 26 cm) made of stainless steel rods (2 mm diam., placed 1 cm apart) connected in series. The animals were prevented from escaping by inverting separate glass beakers over all four of them. The grid floor was connected to a programmable electric shock generator (Medicare Research Stimulator, model SB 44 from Recorders and Medicare Systems, Chandigarh, India). The stimulator was programmed to deliver 360 foot shocks (300 μA) of 2-s duration at intervals of 9 s. The animals were shocked for a total period of 1 h. Control animals were merely placed on the grid under inverted beakers for 1 h but were not shocked. Twenty-four hours after the shock session, behavioral depression was measured by an open field test (OFT) followed by a forced swim test (FST). The OFT was carried out in a circular wooden arena (84 cm diam., 30 cm high) with a white sunmica base with three concentric circles divided into segments by radial lines originating from the centre (25). Each animal was tested for 5 min. Ambulation (locomotor behavior) was measured as the number of lines crossed by an animal, and rearing (exploratory activity) was measured as the number of times the animal stood on its hind limbs with or without the support of the circular wall. In the FST, animals were made to swim individually for 6 min in glass beakers (11 cm diam., 15 cm high) containing fresh water to a height of 6 cm at a temperature of 22 ± 1°C. Each animal made vigorous attempts to get out of the glass beaker during the first couple of minutes and thereafter surrendered to the experimental conditions and became immobile with occasional escape attempts. The total duration of the immobility during the last 4 min of the 6-min test was recorded.

Each drug (imipramine, maprotiline, fluvoxamine, trazodone, alprazolam, or GSH) was administered before shock in one group of animals and immediately after termination of shock treatment in another group to study prevention as well as reversal of shock-induced behavioral depression. Control animals in either case (prevention or reversal of depression) received normal saline (10 ml/kg b.wt., IP). Behavioral effects were measured 24 h later by the OFT and FST as described above.

Assay for Brain GSH Levels

Immediately after behavioral testing, animals were rapidly sacrificed by decapitation and their brains were removed. Different regions of the brain, the cerebral cortex, cerebellum, and brain stem, were dissected out as per the method of Sadasivudu and Lajtha (24); the hypothalamus was dissected out as a single block including the preoptic area. GSH was measured in these regions using DTNB (26). Briefly, weighed amounts of brain tissues were homogenized in 5 ml of cold 0.02 M EDTA. The homogenates were mixed with 4 ml of 50% trichloroacetic acid with intermittent shaking for 10 min and were centrifuged at approximately 6000 rpm for 15 min at 4°C. The supernatant (2 ml) was mixed with 4 ml of 0.4 M Tris buffer (pH 8.9) and 0.1 ml of 0.01 M DTNB. The absorbance was read within 5 min of addition of DTNB using a DU-64 Beckman spectrophotometer at 412 nm against a reagent blank with no homogenate and the total GSH content was calculated using a molar extinction coefficient of 13,100/M/cm.

Statistics

Results are expressed as mean ± SEM. Statistical analysis of the data was performed using the Student's *t*-test or by a one-way analysis of variance (ANOVA) followed by Duncan's multiple range test. The p values equal to or less than 0.05 were adjudged statistically significant.

RESULTS

Behavioral

When measured 24 h later, inescapable foot shock markedly reduced ambulation and rearing scores in the OFT ($p < 0.001$, Student's *t*-test, Table 1) and prolonged swimming-induced immobility duration ($p < 0.01$, Student's *t*-test, Table 1).

Table 2 describes the behavioral effects in mice with various antidepressants and GSH administered before exposure to shock. An overall one-way ANOVA showed significant improvement in ambulation, $F(6, 59) = 7.415$, $p < 0.001$, and rearing, $F(6, 59) = 12.608$, $p < 0.001$, and a decrease in the duration of swimming-induced immobility, $F(6, 61) = 17.839$, $p < 0.001$. A subsequent Duncan's multiple range test revealed that whereas suppression of ambulation by inescapable shock was prevented equally by imipramine, maprotiline, and trazodone, exploratory behavior (as given by the rearing score) was significantly improved by maprotiline, fluvoxa-

TABLE 1

EFFECT OF INESCAPABLE FOOT SHOCK ON BEHAVIOR IN MICE

	OFT		FST
	Ambulation	Rearing	Immobility (s)
Control*	135.25 ± 5.63 (20)	7.3 ± 0.67 (20)	136.36 ± 5.65 (25)
Shocked	87.95 ± 3.49† (20)	3.1 ± 0.69† (20)	158.74 ± 5.60‡ (27)

OFT = open field test; FST = forced swim test. Results are given as mean ± SEM. OFT values represent number of episodes in 5 min and FST values give duration of immobility in 6 min. Numbers in parentheses indicate number of animals.

*Animals were placed on grid but not shocked. †$p < 0.001$ vs. control, ‡$p < 0.01$ vs. control. (Student's t-test).

mine, trazodone, and GSH, with the improvement being most marked with trazodone (Table 2). Similarly, the shock-induced prolongation of immobility in the FST was appreciably decreased by imipramine, fluvoxamine, trazodone, and GSH, with trazodone being the most potent.

As above, highly significant changes were observed in ambulation, $F(6, 56) = 5.195$, $p < 0.001$, rearing, $F(6, 56) = 10.567$, $p < 0.001$, and duration of swimming-induced immobility, $F(6, 58) = 5.158$, $p < 0.001$, when antidepressants or GSH were administered immediately after inescapable shock in mice (Table 3). Thus, ambulation improved with imipramine whereas both ambulation and rearing improved with maprotiline, trazodone, and alprazolam. All the drugs, except maprotiline and GSH, could reverse the immobilizing effects of shock in the FST (Duncan's multiple range test, Table 3).

Biochemical

There was a significant depletion of GSH in the cerebral cortex of mice when measured 24 h after their exposure to inescapable shock ($p < 0.01$, Student's t-test, Table 4). This depletion was only marginal in the hypothalamus and brain stem regions, and the level in the cerebellum was unaffected.

Effects of antidepressants administered before inescapable shock (preshock) on mouse brain GSH levels are given in Table 5. None of the drugs had any appreciable effect on hypothalamic GSH, except maprotiline, which significantly increased the same (Duncan's multiple range test). On the other hand, all the antidepressants significantly increased GSH level in the cerebral cortex when administered prior to shock, $F(5, 46) = 14.071$, $p < 0.001$. Though an increase in the cortical GSH was observed with imipramine, maprotiline, fluvoxamine, trazodone, and alprazolam, the effect was most potent with imipramine and maprotiline (Duncan's multiple range test). In the cerebellum, GSH level was increased only with a preshock administration of imipramine and maprotiline [ANOVA: $F(5, 46) = 13.65$, $p < 0.001$, followed by Duncan's multiple range test]. Brain stem GSH levels remained unaffected.

Table 6 details the effects of postshock administration of antidepressants on brain GSH in mice. Here imipramine enhanced the hypothalamic GSH level [ANOVA: $F(5, 32) = 3.235$, $p < 0.025$ and Duncan's multiple range test]. All the drugs affected cortical GSH, $F(6, 47) = 8.408$, $p < 0.001$. Thus, while imipramine, maprotiline, fluvoxamine, and alprazolam increased shock-depleted cortical GSH, trazodone (20 mg/kg) was exceptional in further reducing the GSH level. Such a depletion was not observed with a smaller dose (10 mg/kg) of trazodone. Cerebellar GSH levels increased with some of the postshock treatments, $F(5, 45) = 9.115$ $p < 0.001$, the effect being specific for imipramine, maprotiline, and fluvoxamine. However, the increase was the highest with imipramine. When administered postshock, at least a few of the antidepressants increased brain stem GSH levels, $F(5, 41) = 5.875$, $p < 0.001$. Thus, equal enhancement of the level was observed with imipramine and maprotiline.

DISCUSSION

Acute uncontrollable stressors have been shown to increase the utilization of NE and 5-HT, leading to reduced levels of the amines in various regions of the brain (3). The behavioral depression following an acute uncontrollable stressor might result from serotonergic mechanisms (7) or may be attributed to a motor activation deficit stemming from reductions of NE (34). It is possible that antidepressants imipramine, maproti-

TABLE 2

BEHAVIORAL EFFECTS OF ANTIDEPRESSANTS GIVEN BEFORE INESCAPABLE FOOT SHOCK IN MICE

			OFT			FST	
No.	Treatment	Dose (mg/kg, IP)	n	Ambulation	Rearing	n	Immobility (s)
1.	Saline	–	18	88.50 ± 04.77	04.16 ± 0.75	20	157.95 ± 05.13
2.	Imipramine	16	08	114.75 ± 09.98*	08.12 ± 1.47	08	120.37 ± 04.75*
3.	Maprotiline	16	08	130.87 ± 06.93*	13.00 ± 3.69*	08	142.50 ± 08.35
4.	Fluvoxamine	10	08	91.75 ± 05.97	12.50 ± 1.21*	08	106.75 ± 05.13*
5.	Trazodone	20	08	141.37 ± 12.03*	25.25 ± 3.27*†	08	85.62 ± 07.87*‡
6.	Alprazolam	02	08	106.50 ± 10.39	08.00 ± 2.11	08	142.37 ± 06.65
7.	Glutathione	500	08	89.62 ± 05.29	10.62 ± 1.16*	08	126.37 ± 09.53*

OFT = open field test; FST = forced swim test; n = number of animals. Results are given as mean ± SEM. OFT values represent number of episodes in 5 min and FST values denote duration of immobility in 6 min.

Significant by one-way ANOVA and Duncan's multiple range test, $p < 0.05$: *vs. 1; †vs. 3,4,7; ‡vs. 2,4,7.

TABLE 3

BEHAVIORAL EFFECTS OF ANTIDEPRESSANTS GIVEN AFTER INESCAPABLE FOOT SHOCK IN MICE

No.	Treatment	Dose (mg/kg, IP)	OFT			FST	
			n	Ambulation	Rearing	*n*	Immobility (s)
1.	Saline	–	10	92.50 ± 07.57	02.50 ± 0.73	15	173.53 ± 06.71
2.	Imipramine	16	10	127.90 ± 06.04*	06.30 ± 1.50	10	134.20 ± 08.62*
3.	Maprotiline	16	10	125.50 ± 06.84*	16.20 ± 3.16*	09	160.22 ± 08.44
4.	Fluvoxamine	10	08	111.75 ± 12.08	03.87 ± 0.64	10	114.30 ± 09.28*
5.	Trazodone	20	08	136.25 ± 10.12*	17.50 ± 2.48*	08	121.62 ± 13.08*
6.	Alprazolam	02	09	122.89 ± 08.18*	17.11 ± 3.15*	08	119.87 ± 13.44*
7.	Glutathione	500	08	82.87 ± 9.57	02.25 ± 1.05	06	154.83 ± 09.67

OFT = open field test; FST = forced swim test; *n* = number of animals. Results are given as mean ± SEM. OFT values represent number of episodes in 5 min and FST values denote duration of immobility in 6 min.
Significant by one-way ANOVA and Duncan's multiple range test, $p < 0.05$: *vs. 1.

line, and fluvoxamine could correct the behavioral depression through a presynaptic uptake inhibition of NE and/or 5-HT. The relative selectivity for the neurotransmitters probably explains why imipramine (affecting both NE and 5-HT uptake) could correct the behavioral deficits in the OFT and FST, when given before as well as after inescapable shock, whereas maprotiline (which is a selective NE uptake inhibitor) and fluvoxamine (which is selective for 5-HT) had only partial effects. Though trazodone is known to have potent central 5-HT antagonist activity (4), at high doses the drug is known to be a weak but specific 5-HT uptake inhibitor (8,23). The 5-HT uptake inhibition combined with a presynaptic α_2-adrenoceptor blockade-mediated potentiation of noradrenergic transmission (5) could explain the antidepressant properties of trazodone in the model of depression due to inescapable shock.

Alprazolam is an agonist of the GABA–ionophore complex that increases GABA activity (27). The GABAergic property of the drug may, at least in part, be responsible for the attenuation of the shock-induced behavioral deficits with the drug when given after shock because decreases in the release of GABA within the hippocampus and 5-HT in the frontal cortex and rectum following inescapable shock are known to lead to the development of behavioral depression (19,20). An interaction with other neurotransmitter systems might have a certain role because benzodiazepine pretreatment has been shown to prevent stressor-induced changes in frontal cortex dopaminergic activity (9).

TABLE 4

EFFECT OF INESCAPABLE FOOT SHOCK ON BRAIN GLUTATHIONE LEVELS IN MICE

Brain Region	Control*	Shocked
Hypothalamus†	1.46 ± 0.09 (8)	1.24 ± 0.11 (7)
Cerebral cortex	1.56 ± 0.04 (16)	1.39 ± 0.03‡ (14)
Cerebellum	1.46 ± 0.06 (12)	1.45 ± 0.06 (14)
Brain stem	0.90 ± 0.04 (16)	0.83 ± 0.04 (14)

Results are given as mean (μmol/g wet wt.) ± SEM. Numbers in parentheses represent sample size.
*Animals were placed on grid but not shocked.
†Hypothalami from two mice were pooled.
‡$p < 0.01$ vs. control (Student's *t*-test).

Consistent with our observation that inescapable foot shock depletes cortical GSH levels, several investigators have shown a reduction in the levels of GSH and total NPSH (nonprotein sulfhydryl) compounds of various tissues in animals subjected to different types of stresses including cold and heat stress (32). Stress activates the sympathoadrenal system with the liberation of adrenaline. Exogenous administration of epinephrine results in hepatic GSH suppression (29). Glycogenolysis occurs in tissues, particularly in the liver, during stress or upon administration of adrenaline. Several investigations have revealed that GSH is concerned with, and is essential for, a number of fundamentally important systems, either acting as a coenzyme (22) or as a firmly bound prosthetic group of one of the glycolytic enzymes, glyceraldehyde-3-phosphate dehydrogenase (13). It is suggested that GSH is involved in glycogenolysis, which leads to a reduction in its level in brain and blood. Thus, catecholamines seem to be logical mediators of stress-induced GSH depletion. The role of other endogenous substances released during acute stress in depleting tissue GSH cannot be overlooked. Cold restraint is known to increase levels of circulating corticosteroids (29). Stress stimulates the hypothalamico-hypophyseo-adrenocortical axis, which in turn liberates adrenocortical hormones. It is suggested that during this process GSH is rapidly oxidized (17) and finally converted to its components glycine and glutamyl cysteine by hydrolysis, with the available glycine contributing towards the synthesis of hippuric acid or other glycine-requiring compounds (32). Endogenous opioid peptides may also be elevated during stress (14), and stimulation of central opioid receptors by peptide agonists can result in decreases in glutathione concentrations in the liver (11).

An alternative explanation for the observed loss in brain glutathione could run as follows. The turnover of monoamines by monoamine oxidase (MAO), a mitochondrial enzyme, is associated with the formation of a cellular oxidant, hydrogen peroxide (H_2O_2). The H_2O_2 thus generated is scav-

TABLE 5

EFECT OF PRESHOCK ADMINISTRATION OF ANTIDEPRESSANTS ON BRAIN GLUTATHIONE LEVELS IN MICE

No.	Treatment	Dose (mg/kg, IP)	Hypothalamus*	Cerebral Cortex	Cerebellum	Brain Stem
1.	Saline	–	1.27 ± 0.08 (10)	1.27 ± 0.05 (12)	1.49 ± 0.03 (12)	0.85 ± 0.03 (12)
2.	Imipramine	16	1.38 ± 0.15 (05)	1.65 ± 0.03†‡ (08)	1.92 ± 0.07† (08)	0.83 ± 0.05 (08)
3.	Maprotiline	16	1.73 ± 0.14† (06)	1.77 ± 0.08†‡ (08)	1.99 ± 0.12† (08)	0.86 ± 0.06 (08)
4.	Fluvoxamine	10	1.37 ± 0.19 (06)	1.48 ± 0.05† (08)	1.37 ± 0.08 (08)	0.94 ± 0.04 (08)
5.	Trazodone	20	1.36 ± 0.07 (06)	1.42 ± 0.03† (08)	1.48 ± 0.08 (08)	0.96 ± 0.05 (07)
6.	Alprazolam	02	1.54 ± 0.04 (06)	1.48 ± 0.02† (08)	1.45 ± 0.03 (08)	0.80 ± 0.07 (08)

Results are given as mean (μmol/g wet wt.) ± SEM. Numbers in parentheses represent sample size.
*Hypothalami from two mice were pooled.
Significant by one-way ANOVA and Duncan's multiple range test, $p < 0.05$: †vs. 1; ‡vs. 4,5,6.

enged by GSH peroxidase, leading to the formation of GSH disulfide (GSSG) (16). Thus,

$$\text{monoamine} + O_2 + H_2O \xrightarrow{\text{MAO}} H_2O_2 + NH_3 + \text{corresponding aldehyde}$$

$$H_2O_2 + 2GSH \xrightarrow{\text{GSH peroxidase}} GSSG + 2\,H_2O.$$

Normally GSSG is efficiently reduced by GSH reductase:

$$GSSG + NADPH + H^+ \xrightarrow{\text{GSSG reductase}} 2GSH + NADP^+.$$

However, this is hampered during exposure of tissues to added peroxides or peroxide-generating cell toxins (1,31), leading to a decrease in tissue GSH. Therefore, increased utilization of monoamines following an acute uncontrollable stressor could in theory be associated with an oxidative stress due to the accumulation of H_2O_2 with the subsequent consumption of tissue GSH. This explanation seems particularly relevant in the light of our results with imipramine, maprotiline, and fluvoxamine on shock-induced brain GSH depletion. All these drugs were able to prevent as well as reverse the GSH depletion in the cortex. These drugs are monoamine reuptake inhibitors. Because MAO is found in, or attached to, the membrane of the intraneuronal mitochondria, reuptake of monoamines

TABLE 6

EFECT OF POSTSHOCK ADMINISTRATION OF ANTIDEPRESSANTS ON BRAIN GLUTATHIONE LEVELS IN MICE

No.	Treatment	Dose (mg/kg, IP)	Hypothalamus*	Cerebral Cortex	Cerebellum	Brain Stem
1.	Saline	–	1.39 ± 0.06 (10)	1.40 ± 0.03 (10)	1.49 ± 0.03 (10)	0.82 ± 0.04 (10)
2.	Imipramine	16	1.79 ± 0.15† (05)	1.71 ± 0.06† (08)	1.97 ± 0.06†‡ (08)	1.08 ± 0.08† (08)
3.	Maprotiline	16	1.48 ± 0.15 (05)	1.62 ± 0.05† (06)	1.73 ± 0.07† (06)	1.12 ± 0.05† (08)
4.	Fluvoxamine	10	1.39 ± 0.05 (06)	1.58 ± 0.08† (08)	1.69 ± 0.08† (08)	0.82 ± 0.07 (08)
5.	Trazodone	20	1.21 ± 0.06 (06)	1.19 ± 0.06† (06)	1.36 ± 0.11 (06)	0.77 ± 0.08 (06)
6.	Trazodone	10	–	1.46 ± 0.07 (08)	–	–
7.	Alprazolam	02	1.37 ± 0.13 (06)	1.59 ± 0.02† (08)	1.61 ± 0.07 (07)	0.96 ± 0.05 (07)

Results are given as mean (μmol/g wet wt.) ± SEM. Numbers in parentheses represent sample size.
*Hypothalami from two mice were pooled.
Significant by one-way ANOVA and Duncan's multiple range test, $p < 0.05$: †vs. 1; ‡vs. 3,4.

into nerve endings is necessary for MAO to deaminate the monoamines (33). The deamination was thus blocked by the above drugs by virtue of their monoamine uptake inhibition, thereby decreasing both the rate of peroxide formation and the utilization of GSH. That monoamine uptake is linked to GSH levels is further strengthened by the findings with trazodone. Trazodone is not known to have any definite monoamine uptake inhibition, though at very high doses it is known to be a weak but selective uptake inhibitor of 5-HT (23). However, the drug is reported to increase NE turnover in the rat brain (10), which could lead to accumulation of peroxides and a subsequent utilization of GSH. It may be argued that the NE-releasing properties coupled with an absence of monoamine uptake inhibition with trazodone resulted in a further reduction of GSH in shocked mice.

It is well known that most stresses have an associated psychic component and that a number of stress-induced changes are mediated through the hypothalamus (32). By calming the animals, alprazolam might have reduced the psychic component of stress and thus minimized the shock-induced reduction in GSH levels.

To conclude, there appears to be a certain correlation between cortical GSH levels and behavioral depression due to inescapable shock. Whether this is a feature specific for animal models of depression using stress as a predisposing factor or whether there is a direct link between tissue levels of GSH and the disease depression needs further corroboration. But the present data, especially with those antidepressants that act through monoamine reuptake inhibition, seem to suggest that depression from stress is associated with an accelerated utilization of monoamines effecting an increase in peroxides and a decrease in the levels of GSH, a peroxide scavenger.

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