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Plasma Catecholamine and Corticosterone as Well as Brain Catecholamine Changes During Coping in Rats Exposed to Stressful Footshock[1]

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SWENSON, R. M. AND W. H. VOGEL. *Plasma catecholamine and corticosterone as well as brain catecholamine changes during coping in rats exposed to stressful footshock.* PHARMACOL BIOCHEM BEHAV 18(5) 689–693, 1983.—Rats received 60 minutes of footshock that was escapable (coping group) or inescapable (noncoping group). Plasma taken by jugular catheter showed that noncoping rats, compared with coping rats, had significantly higher peak norepinephrine (NE) and epinephrine (E) concentrations and significantly longer elevation of these catecholamines after footshock. Similarly, plasma corticosterone levels remained elevated significantly longer after footshock in noncoping rats. In brain, hypothalamic NE concentrations were lower in noncoping rats compared with coping controls, and this difference remained for at least 30 minutes after shock. A fall in hippocampal NE concentration was seen only in coping rats once they learned to terminate shock. Our data indicate that neurochemical changes can be separated into changes due to the aversive nature of the stimulus and the ability to cope with a stressor. The inability to cope augments plasma catecholamine increases in response to a stressor and prolongs their return to baseline values. The latter is also true for corticosterone levels. The decrease in hippocampal NE in coping and the decrease in hypothalamic NE in noncoping rats is not due to footshock by itself but to the ability of the rat to terminate this stressor. No strong correlation between central and peripheral catecholamine changes became apparent except a possible negative correlation between hypothalamic NE and peripheral NE and E levels.

Stressful footshock Catecholamine Corticosterone Coping

CHANGES in peripheral and central catecholamines (CA) and plasma corticosterone of animals during exposure to various stressors have been studied thoroughly. Peripheral CA levels rise rapidly at the onset, remain very high during, and return to baseline values after termination of a stressor [4,17]. Under these circumstances, plasma epinephrine is derived mostly from the adrenal medulla, whereas plasma norepinephrine originates mostly from sympathetic nerves with a sizeable contribution from the adrenal medulla [11]. Increases in the levels of plasma corticosterone released from the adrenal cortex are slower in onset, lower in magnitude, and a less sensitive index of stress [14,22]. In the CNS, individual CAs remain unchanged, rise, or fall depending on the individual amine, the brain area studied, or the stressor employed [6, 7, 27, 28]. In most of these studies, animals had no control over, or could not cope with, the stressor because they were restrained, exposed to cold temperatures, or received inescapable footshock.

However, the ability to control a stressful situation, or to cope successfully with a stressor, has significant consequences on the response of the organism. The few data available show higher concentrations of norepinephrine (NE) in whole brain, hypothalamus, brainstem, and anterior cortex for coping versus noncoping rats in a stressful situation [26–29]. These data have been determined, in large part, after long periods of stress, and few data are available after shorter periods of stress. Furthermore, no plasma CA or corticosterone levels have been determined in catheterized rats able to cope with the identical stressor.

Determination of catecholamine and corticosterone levels in coping and noncoping rats under the identical stressful situation may help elucidate the components of stress that are due to the aversive nature of the stimuli or due to the inability of the organism to cope with the stressor. In addition, such studies may suggest a correlation between central and peripheral CA changes that would be helpful for human

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studies where peripheral, but not central, catecholamines can be measured. For these reasons, we studied plasma norepinephrine (NE), epinephrine (E) and corticosterone (C) before, during, and after 60 minutes of footshock in coping and noncoping rats. In addition, NE, E and dopamine (DA) concentrations in hypothalamus and hippocampus were measured in other groups of rats exposed to the same stressful situation.

METHOD

Male Sprague-Dawley rats weighing about 275 g were housed together for one week and then randomly assigned to one of three groups. The first group consisted of unshocked control animals. These animals were treated like the following 2 groups but never received shock. Animals of the second and third groups were grouped in pairs and received footshock with one rat controlling (coping group) the duration of shock for itself and the yoked animal (noncoping group). During this time, animals received food and water ad lib.

Footshock was given in a BRS/LVE (#RSC-044) rat shuttle box bisected by a metal partition across the long axis of the cage. The floor was fixed in place and two manipulanda (ceiling pole and paddle) presses were required to terminate shock, and shock could not be avoided. The left hand compartment was used for all control shock subjects, the right side for rats with no control over shock. Grids in both compartments were wired in series to a shock scrambler and regulated shock source (LVE 113-04). The shock was unsignaled and occurred after irregular intervals of 5 to 15 sec. If not terminated, the shock lasted 10 sec. The amount of shock received by both rats depended on the speed with which the coping rat terminated shock. Coping rat responses were shaped for pole or paddle pressing during the first 15 minutes of the 1 hr trial and, typically, rats learned to terminate the shock within this time. Both rats received approximately 250 footshocks (1 mA) for a total of approximately 500 seconds of shock during the 1 hr trial.

For blood measures, catheters were placed in the external jugular vein and passed into the vena cava of anesthesized (Ketamine plus pentobarbital) animals 2 days before the experiment; previous studies have shown that rats recover from this procedure within 2 days. The catheters were kept patent with the use of heparin/saline (1000 IU/ml). Blood samples (about 0.25 ml) were drawn while the rats were in the home cage (−15 min or 15 min prior to stressor onset), just before shock onset in the shock apparatus (0 min), and after 1, 5, 15, 30, and 60 min during shock. Animals remained in the shock apparatus and blood was collected 30 minutes after termination of shock or after 90 minutes of the experiment. Rats were then returned to their home cage where a final blood sample was taken 3 hours after the termination of footshock or 240 min of the experiment. The blood volume withdrawn for catecholamine assay was replaced by saline with heparin (100 IU/ml). Plasma samples were stored at −70°C for not longer than 2 months.

For brain catecholamines, sets of rats were exposed to the identical controllable and uncontrollable footshock stressor and decapitated at the specified times. Their brains were dissected immediately on ice into hypothalamus and hippocampus. Control animals were catheterized, nonshocked rats. Samples were wrapped in foil and placed on dry ice immediately after dissection. Samples were stored at −70°C for not longer than 2 months.

Plasma and brain catecholamines were determined by the radioenzymatic technique using commercial kits (Upjohn Diagnostics, Kalamazoo, MI). This test works very well; specificity is high, sensitivity is in the pg range and variability is less than 10%.

Plasma corticosterone levels were determined by the fluorometric procedure of Glick *et al.* [5].

The number of animals listed in our tables varies because of loss of animals due to biting of the catheter during the experiment, omission of strongly hemolysed samples that could interfere with Ca determinations, or loss of particular samples during analysis.

Statistical evaluations were performed by using the *t*-test for independent samples.

TABLE 1

PLASMA NOREPINEPHRINE (pg/ml) IN RATS RECEIVING FOOTSHOCK

Time (min)	NS	C	NC
−15	177 ± 42 (5)	170 ± 52 (4)	154 ± 16 (11)
0	270 ± 58 (6)	219 ± 50 (6)	213 ± 57 (11)
1^S	262 ± 66 (5)	459 ± 40* (5)	601 ± 119* (10)
5^S	230 ± 38 (5)	402 ± 79* (6)	818 ± 189*† (11)
15^S	172 ± 25 (5)	460 ± 66* (6)	868 ± 156*† (11)
30^S	282 ± 127 (4)	556 ± 157* (6)	756 ± 118* (11)
60^S	266 ± 41 (6)	414 ± 135 (6)	546 ± 95* (11)
90	214 ± 35 (5)	401 ± 144 (6)	363 ± 62 (11)
240	———	200 ± 28 (5)	225 ± 33 (6)

NS: no shock rats; C: coping rats; NC: noncoping rats; S: shock.
Each value represents the means ± SEM.
Values in parentheses represent number of animals.
*$p<0.05$, comparison with −15 min value.
†$p<0.05$, comparison between C and NC values.

RESULTS

Rats that could control the shock did so reliably within 15 min causing subsequent shocks for both pairs to be approximately 1–2 seconds in duration. Most rats preferred the pole instead of the paddle and poised themselves near it. At shock onset they pressed the pole twice rapidly. Rats without control over shock initially ran about the cage vocalizing but soon accepted shock in a passive fashion.

Table 1 shows that repeated blood sampling and exposure to the apparatus in unshocked rats had no significant effect on plasma NE concentrations. However, NE rose significantly in both shocked groups within 1 minute of shock onset. Plasma NE remained significantly higher than baseline for 30 min in the coping rats. Noncoping rats had higher plasma NE levels at 5 and 15 min compared with the coping animals, and these levels remained elevated slightly longer. At 3 hours after termination of shock, both groups had plasma NE concentrations similar to baseline values.

The ability to control shock had the more striking effect on plasma E (Table 2). In rats that controlled shock, plasma E was significantly elevated above baseline at 1, 5, 15, and 30 minutes. Baseline values were reached again by the end of the footshock period. In rats without control over shock, plasma E showed a similar sharp rise at one minute with significantly higher values over baseline as well as over those of the shocked control at 5, 15, 30, 60 and 90 minutes.

TABLE 2

PLASMA EPINEPHRINE (pg/ml) IN RATS RECEIVING FOOTSHOCK

Time (min)	NS	C	NC
−15	62 ± 71 (5)	105 ± 34 (5)	128 ± 25 (10)
0	144 ± 30 (6)	155 ± 69 (5)	174 ± 67 (10)
1^S	150 ± 68 (5)	404 ± 60* (5)	666 ± 111* (10)
5^S	170 ± 65 (5)	323 ± 87* (5)	876 ± 203*† (11)
15^S	129 ± 57 (5)	502 ± 102* (5)	920 ± 142*† (11)
30^S	72 ± 26 (4)	258 ± 46* (5)	843 ± 137*† (10)
60^S	184 ± 68 (5)	141 ± 32 (5)	538 ± 114*† (11)
90	141 ± 51 (5)	87 ± 11 (5)	318 ± 72*† (10)
240	———	45 ± 13 (5)	34 ± 5* (6)

NS: no shock rats; C: coping rats; NC: noncoping rats; S: shock.
Each value represents the mean ± SEM.
Values in parentheses represent number of animals.
*$p<0.05$, comparison with −15 min value.
†$p<0.05$, comparison between C and NC values.

TABLE 3

PLASMA CORTICOSTERONE (μg/100 ml) IN RATS RECEIVING FOOTSHOCK

Time (min)	NS	C	NC
−15	22.3 ± 3.4 (5)	18.3 ± 3.9 (5)	18.0 ± 3.7 (9)
0	18.6 ± 2.3 (4)	25.0 ± 2.6 (7)	24.4 ± 3.7 (8)
5^S	19.0 ± 2.9 (4)	30.7 ± 2.2* (8)	37.8 ± 4.2* (9)
15^S	18.9 ± 3.6 (4)	32.1 ± 2.5* (5)	33.3 ± 3.2* (11)
30^S	———	35.3 ± 1.9* (4)	39.5 ± 2.5* (9)
60^S	20.4 ± 5.6 (4)	28.6 ± 2.1* (5)	38.5 ± 3.0* (8)
90	24.1 ± 2.7 (5)	20.0 ± 4.8 (4)	41.3 ± 6.9*† (6)
240	15.1 ± 3.9 (5)	26.6 ± 5.1 (6)	38.3 ± 3.8*† (9)

NS: no shock; C: coping rats; NC: noncoping rats; S: shock.
Each value represents the means ± SEM.
Values in parentheses represent number of animals.
*$p<0.05$ comparison with −15 min value.
†$p<0.05$ comparison between C and NC values.

TABLE 4

NOREPINEPHRINE AND DOPAMINE (ng/g) IN HYPOTHALAMUS IN RATS RECEIVING FOOTSHOCK

	Norepinephrine		Dopamine	
Time (min)	C	NC	C	NC
0	1632 ± 72 (6)		386 ± 22 (5)	
10^S	1376 ± 151 (5)	1289 ± 129 (4)	341 ± 39 (5)	281 ± 23* (4)
60^S	1777 ± 82 (5)	1166 ± 126*† (4)	382 ± 64 (4)	446 ± 101 (3)
90	1346 ± 155 (4)	962 ± 145* (4)	295 ± 42 (7)	458 ± 62† (7)
240	1330 ± 145 (6)	1309 ± 165 (6)	566 ± 70* (6)	515 ± 66 (6)

C: coping rats; NC: noncoping rats; S: shock.
Each value represents the mean ± SEM.
Values in parentheses represent number of animals.
*$p<0.05$ compared with non-shocked controls (0 time).
†$p<0.05$ compared with coping controls.

At 3 hours after termination of the shock both groups showed lower than baseline E levels that became significant only in the noncoping rats. Rats that did not receive shock showed no significant plasma E changes during the time of the experiment.

Table 3 shows the effects of coping and noncoping on corticosterone levels. Plasma corticosterone concentrations in unshocked controls remained constant over the time period studied. Coping and noncoping rats showed an increase in corticosterone levels following footshock. This increase was considerably longer lasting in the noncoping animals.

NE and DA concentrations in hypothalamus in unshocked, coping and noncoping rats are depicted in Table 4. Rats with control over shock were not different in their NE levels from the unshocked controls (time=0) at any time period of the experiment. Rats without control over shock showed a progressive depletion of NE in the hypothalamus that was statistically significant at the 60 and 90 minute periods compared with the unshocked and coping animals. At 3 hours after the termination of footshock, NE concentrations in noncoping rats were not different from nonshocked controls. Noncoping rats had significantly lower DA levels compared with unshocked rats ten minutes after shock onset, but they were not different from coping rats. Thirty minutes after the end of the shock trial (90 min), hypothalamic DA concentrations of noncoping rats were significantly higher than those of the coping rats but were not different from the unshocked rats. Coping rats showed a significant increase in DA concentration by 3 hours (240 min) after the termination of shock. No significant differences were found between groups for E in hypothalamus at any time during the experiment. The average E concentration in hypothalamus was 52±19 ng/g for unshocked controls.

NE concentrations in the hippocampus are listed in Table 5. Baseline values are shown at time 0. Coping or noncoping

TABLE 5

NOREPINEPHRINE (ng/g) IN HIPPOCAMPUS OF RATS RECEIVING FOOTSHOCK

Time (min)	C	NC
0	133 ± 6 (6)	
10^S	118 ± 5 (5)	109 ± 12 (5)
60^S	97 ± 13* (4)	150 ± 26 (4)
90	158 ± 28 (4)	131 ± 25 (5)
240	212 ± 22 (6)	258 ± 34 (6)

C: coping rats; NC: noncoping rats; S: shock.
Each value represents the mean ± SEM.
Values in parentheses represent number of animals.
*$p<0.05$ compared with non-shocked controls (0 time).

groups were not different from nonshocked animals except for a decrease in NE levels in coping rats. No differences were seen in E and DA values among the groups. The average concentrations of E and DA in the hippocampus for unshocked controls were 5.7±0.6 ng/g and 122±16 ng/g, respectively.

DISCUSSION

This study investigated catecholamine concentrations in plasma and in hypothalamus and hippocampus as well as plasma corticosterone levels before, during and after exposure of rats to footshock that could or could not be terminated. Both rats received the same aversive stressor in our design, that is, the identical number of equally intense footshocks. However, the psychological impact of this stressor was different. One rat could terminate or cope with the stressor, whereas the yoked rat (noncoping) could not terminate or cope with the stressor.

In our experiments, plasma NE concentrations rose in both coping and noncoping rats due to the aversive nature of the stressor. However, the noncoping rats experienced considerably higher and longer lasting increases in NE. This difference became even more apparent with E; concentrations of this catecholamine increased even more and stayed elevated longer in noncoping animals. Thus, plasma catecholamine concentrations rise in response to footshock in both groups, but noncoping rats showed higher responses that lasted longer. This difference was particularly striking for E. This difference probably reflects the "emotional" component of the inability to cope because in human studies it was shown that higher and longer-lasting increases in plasma E were indicators of uncertainty and anxiety [1].

Corticosterone levels also increased during footshock although increases were considerably less than those seen with the catecholamines. Similar to plasma CA, C levels remained elevated considerably longer in noncoping as compared to coping rats. Similar findings have been reported in rats subjected to considerably longer periods of shock; after the first 5 hr of stress the noncoping rats were higher than the coping rats, but this difference had disappeared 5 hr following cessation of 19 hr of stress [25].

In the hypothalamus, no significant differences between coping and noncoping rats were apparent until the end of the shock session when noncoping rats showed decreased norepinephrine levels. Weiss [27] in his studies of coping also reported significant reductions of hypothalamic NE in noncoping rats at 30 minutes after shock termination, a difference that lasted for at least 24 hours. Our NE data at 3 hours after termination of footshock, however, showed no difference between coping and noncoping rats in hypothalamus. In our study, footshock was given for one hour, whereas Weiss stresses his animals for much longer periods of time via tail electrodes. Thus, although coping has a similar effect on brain norepinephrine during either long or short stress sessions, the length of time required for this effect to disappear seems dependent on the duration of the stress session. Dopamine concentrations in the hypothalamus appear to fall and then to rebound to supranormal levels in both shocked groups. This sequence of events seems delayed in the coping group. Weiss [26] also reports that dopamine in hypothalamus is significantly higher in noncoping rats compared with unshocked controls 30 minutes after shock termination. E levels were unaffected by the ability or inability to terminate the footshock. This is in contrast to acute cold swim stress which lowers hypothalamic E or chronic oscillation stress which increases hypothalamic E [18].

In the hippocampus, no difference in norepinephrine was found except at the end of the footshock period when lower levels were seen in the coping compared with the noncoping rats. This difference was not seen in the first 10 min of shock, a time when coping rats had not mastered the task. It had disappeared 30 minutes after termination of shock. Because the hippocampus is implicated in learning [21], it is tempting to speculate that this neurochemical change in coping rats is a reflection of the learning process where shock termination is contingent on their behavior. The hippocampus is prominently connected to the hypothalamus via the fornix, and lesion of the fornix block some stress related changes in the hypothalamus [20] as well as stress related behaviors [8]. The fall in NE of the hippocampus in coping rats may act like a fornical lesion by preventing a fall in hypothalamic NE.

It is well known that different stressors can produce a variety of neurochemical changes in the stressed organism. Often, these changes are attributed to the aversive nature of the stressor. However, studies using rats that can or cannot cope with the stressor show that the ability to control the stressor is perhaps even more important than its noxious nature. Rats that gain predictability or control over stressors do not show the marked decreases in norepinephrine in certain brain areas that are apparent in rats without control [26, 28, 29]. Similarly, serotonin concentrations in the septum and anterior cortex decrease in noncoping rats, whereas coping rats show no changes or even increases in the levels of this amine in response to the same stressor [16].

Our results show that increases in plasma catecholamine and corticosterone levels remain elevated longer in noncoping as compared with coping rats. Thus, it appears that peripheral stress-related changes can be minimized and shortened by gaining control over the stressor or they can be augmented and prolonged by the inability to cope with the same stressor.

The ability or inability to cope with identical stressors can lead to a variety of physical and behavioral pathologies [3, 9, 10, 25]. Under our experimental conditions, coping rats escape a later footshock quickly, whereas most noncoping rats take more time or do not escape at all [24]. This is similar to other studies where animals given uncontrollable shock perform more poorly [10, 19, 24, 27]. This behavioral syndrome that follows an unpredictable, inescapable stressor has been called "learned helplessness" and has been defined as an

inability to learn a novel response and the passive acceptance of a painful stressor [10]. "Learned helplessness" has been proposed as a model for human depression, and behavioral, biochemical, and pharmacological data are available to support such a proposal [10, 19, 26]. Our data also support this model. The inability to cope, and not the stressor per se, produces the after-effects, a situation that is similar to the role of "life events" in the etiology of human depression [13]. The higher and longer-lasting levels of plasma catecholamines, in particular E and of corticosterone in noncoping rats, are similar to those seen in depressed patients [1, 2, 12]. Finally, the reduced levels of brain NE seen only in noncoping, later helpless, animals is consistent with the biogenic amine hypothesis of depression [12]. However, more data are needed to correlate more firmly this model with human depression.

A comparison between central and peripheral catecholamine levels revealed no striking correlations. A possible correlation could be postulated for the hypothalamus and plasma CA levels. In control rats, hypothalamic NE and plasma CA concentrations were at resting levels. In coping rats, hypothalamic NE levels decreased slightly, although not significantly, and the rise in peripheral catecholamines was moderate and short-lived. In noncoping animals, hypothalamic NE levels decreased significantly and plasma NE and E levels were more markedly elevated and remained higher longer. Thus, a possible negative correlation between hypothalamic NE and plasma NE and E levels might exist.

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