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Stress induces rapid changes in central catecholaminergic activity in *Anolis carolinensis*: Restraint and forced physical activity

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Abstract

Immobilization stress and physical activity separately influence monoaminergic function. In addition, it appears that stress and locomotion reciprocally modulate neuroendocrine responses, with forced exercise ameliorating stress-induced serotonergic activity in lizards. To investigate the interaction of forced physical activity and restraint stress on central dopamine (DA), norepinephrine (NE), and epinephrine (Epi), we measured these catecholamines and their metabolites in select brain regions of stressed and exercised male *Anolis carolinensis* lizards. Animals were handled briefly to elicit restraint stress, with some lizards additionally forced to run on a track until exhaustion, or half that time (50% of average time to exhaustion), compared to a control group that experienced no restraint or exercise.

Norepinephrine concentrations in the hippocampus and locus ceruleus decreased with restraint stress, but returned to control levels following forced exhaustion. Levels of NE in the raphé nuclei and area postrema, and epinephrine in raphé became elevated following restraint stress, and returned to control levels following forced physical activity to 50% or 100% exhaustion. Striatal DA increased as animals were exercised to 50% of exhaustion, and returned to baseline with exhaustion. At exhaustion, striatal Epi levels were diminished, compared with controls. In the area postrema, exhaustion reversed a decline in epinephrine levels that followed forced physical activity. These results suggest that stress stimulates a rapid influence on central catecholamines. In addition, forced exercise, and even exhaustion, may alleviate the effects of restraint stress on central monoamines.

Keywords: Dopamine; Norepinephrine; Epinephrine; Lizard; Exercise; Exhaustion

1. Introduction

Activity and exercise, both forced and voluntary, increase the function of dopaminergic systems in the striatum [28,42–44,78]. Other central catecholaminergic systems, including norepinephrine (NE) and epinephrine (Epi), are also influenced by exercise [3,6,8,10,13,25,38,56,59,64]. Norepinephrine concentrations in the pontine–medullary region, where central catecholamines are synthesized, are increased both by voluntary activity wheel exercise and forced treadmill activity in rats, with a concomitant increase in the NE/Epi catabolite MHPG in terminal regions such as the frontal cortex and hippocampus of treadmill trained rats [27].

The relationship between activity and stress is complicated by the fact that exercise, especially forced physical activity, can be stressful in itself [29,69,80,81], but exercise can also ameliorate the effects of other stressors [11,18,19,21,29,40,68,69]. Plasma glucocorticoid levels rise for 25 min (females) to 40 min (males) during forced exercise in mice [16]. However, in rats, exercise training reduces the response of the hypothalamo-pituitary adrenocortical axis (HPA) to acute exercise at the level of corticotropin (ACTH)

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in the pituitary [19], and increased NE concentrations in the hypothalamus [20]. Non-exercise stressors, such as restraint or aggression, have also been demonstrated to elicit significant responses from central catecholaminergic systems [46,50,82]. Combined, these data suggest an interaction between or shared use of the pathways of the central catecholaminergic neural regulatory systems for stress and locomotor activity. Support for this comes from the observation that similar responses of central catecholamines are seen with physical activity and restraint stress [20]. Additionally, central catecholamine levels modulate serotonergic activity in the raphé [30,31], which plays a role in the neuroendocrine response to both physical and restraint stress [29].

In the lizard *Anolis carolinensis*, a similar co-regulation between stress and locomotor neurocircuitry influences central serotonergic activity [29]. While forced physical activity increased serotonergic activity in the raphé, evidence that forced activity ameliorated restraint stress-induced elevation of serotonergic activity was seen in subiculum, nucleus accumbens, striatum, and area postrema. The neurotransmitter systems that mediate both motor activity and stress responsiveness are coordinated [18], and need to be for two reasons: regulation of glucocorticoid secretion to manage both energetic needs and stress reactions, plus acquisition of contextual significance to the interaction between locomotion and stress. For example, forced exercise that results from fleeing a predator should be stressful early, but should also help to ameliorate the stress response as the threat is diminished. We have hypothesized that rapid neural and endocrine responses correlate with the ability of an individual to cope with stress [29,60,71,72,74,76], and currently extend this hypothesis to include physical stress, as measured by running.

The primary purpose of this study was to explore the effects of forced physical activity and restraint stress on the central catecholaminergic systems in the lizard *A. carolinensis*. We examined concentrations of dopamine (DA), NE and Epi in the hippocampus, nucleus accumbens, raphé, locus ceruleus, and area postrema; as monoaminergic activity in these nuclei are known to respond to stress and or exercise [1]. We hypothesized that stress and physical activity interact via evoked monoaminergic responses within specific brain regions that are elements in an overlapping neurocircuitry.

2. Materials and methods

2.1. Animals

Adult male (>60 mm snout–vent length) *A. carolinensis* were obtained commercially (Glades Herp, FL). Each was weighed, measured and placed individually into a 5 gal glass vivarium containing a wooden perch. All lizards were watered and fed (crickets) ad libitum. Lights and temperature were regulated to maintain gonadal activity (14 h light on at 06:00 h, 32 °C:10 h dark, 20 °C) [51], and relative humidity was kept at approximately 75% [70,73]. Lizards were acclimated to cages for at least one week before experiments began. The procedures and care of animals were carried out in accordance with the Declaration of Helsinki and with the National Institute of Health Guide for the Care and Use of Laboratory Animals under the approval of the University of South Dakota IACUC.

2.2. Experimental design: stress and exercise

Following acclimation, reproductively responsive males were divided into four treatment groups ($n = 8$ each): (1) control (no handling, no exercise), (2) restraint stress (handling, no exercise), (3) exercise to 50% exhaustion (following restraint), and (4) complete exhaustion (also following restraint). There were no significant differences in mean initial body mass or snout–vent length between groups. Restraint stress was administered by holding the lizard for 25 s. This kind of physical restraint has been demonstrated to stimulate central catecholamines, indoleamines and plasma corticosterone in *A. carolinensis* at 25 s, 30 s, 90 s, and 300 s [32,33,52,79]. Lizards (with the exception of controls) were placed at the starting strip of a track fashioned from a large, hard rubber basin with laminated plastic covering on the sidewalls. A similarly laminated barrier was placed concentrically, giving the track a circumference of 37.7 cm, width of 12.0 cm, and height of 23.5 cm. A yellow stripe signified the starting point, and three blue stripes represented quarter points of the track. Restrained animals were also briefly placed on the track to control for stress due to exposure to a novel environment. Forced physical activity consisted of placing lizards on the track following restraint and prodding on the tail with a paintbrush to induce running. Complete exhaustion was defined as the point at which the animal refused to move after 60 s of prodding. The average time to complete exhaustion was 25 min. The group representing 50% exhaustion was sampled after half the average time to complete exhaustion (12.5 min). Lizards were killed by rapid decapitation immediately following application of stress (restraint), 50% and complete exhaustion, or after removal from cages (control).

2.3. Preparation of brain tissue

Brains were rapidly removed and placed on dry ice/ice mixture within 15 s of capture. Brains were then serially sectioned at 300 μm, thaw mounted on glass slides and refrozen for microdissection. Brains regions were identified using a stereotaxic atlas and map of catecholaminergic immunoreactivity in the *A. carolinensis* brain [39,53], and microdissected with a 300 μm diameter punch [75]. Regions chosen for analysis included the hippocampus, nucleus accumbens, striatum, raphé, locus ceruleus, and area postrema. Brain regions were chosen based on behavioral significance, involvement

in motor activity or exercise [7,28,44], and/or stress response [29], and on homologies to mammalian systems [9].

2.4. Analysis of monoamines

Dopamine, its metabolite homovanillic acid (HVA), epinephrine, and norepinephrine were measured using high performance liquid chromatography (HPLC) with electrochemical detection [29,75]. Briefly, the punched samples were expelled into 60 μl of a sodium acetate buffer (pH 5) containing α-methyl dopamine (internal standard), freeze–thawed and centrifuged at 15,000 × *g* for 2 min. Prior to centrifugation, 2 μl of a 1 mg/ml ascorbate oxidase solution (Boehringer Mannheim) was added to each sample. The supernatant was removed and 45 μl was injected into a chromatographic system (Waters Associates, Inc.) and analyzed electrochemically with an LC-4B potentiostat (Bioanalytical Systems). The electrode potential was set at +0.6 V with respect to an Ag/AgCl reference electrode. The pellet was dissolved in 100 μl of 0.2N NaOH and protein content was assayed [9].

2.5. Interpretation of data

Although neurotransmitter levels, expressed as pg amine/μg protein, are apparently uncomplicated, understanding relative changes in activity of monoamine systems often requires some interpretation. Accessible transmitter concentration is often greater than demand for individual or even multiple behavioral events; hence, monoamine levels often remain unchanged. Constant transmitter concentrations may also occur when synthesis is rapidly elevated in response to stimulus or stress, as production may offset release. Thus, when there has been sufficient time following behavioral or environmental stimulus, data are often presented as ratios of catabolite to transmitter (e.g. HVA/DA), which is an estimate of monoaminergic turnover. As such, the activity of a given monoamine system can be said to increase as the ratio increases, which is more often than not, a result of changes in catabolite levels.

On the other hand, sampling that immediately follows behavior may discriminate a reduction in transmitter concentrations reflecting recent release. Additionally, when rapid synthesis or reuptake of transmitter coincides with extensive release and catabolism, both monoamine transmitter and catabolite concentrations are likely to rise. While this clearly indicates an increase in system activity, the ratio remains unchanged and is not valuable for determining monoaminergic activity. Second, measurements closely following stimuli, during a period when transmitter synthesis is rising, may reflect increased concentrations of transmitter from synthesis and uncatabolized contemporary release, as may occur with a brief restraint stress. To allow for this, the current study reports levels of monoamine, rather than an overall ratio. These measurements were compared across treatment groups by analysis of variance, followed by Duncan's multiple range tests.

3. Results

Catecholaminergic systems in the hippocampus, locus ceruleus, raphé, and area postrema, but not in the striatum, were influenced by a brief restraint stress (Table 1). Forced physical activity modified these systems in striatum and area postrema. Exercise reversed the effects of restraint stress in locus ceruleus, raphé, and area postrema. Exhaustion reversed the effects of restraint stress in locus ceruleus and

Table 1
Comparison of changes in monoamine concentration by brain region in male lizards following: (1) 25 s restraint stress, then (2) forced activity to 50% exhaustion, and then at (3) exhaustion

Treatment	Monoamine	Hippocampus	Striatum	Locus ceruleus	Raphé	Area postrema
Restraint stress	5-HT	↓	↓	↓	–	↑ 5-HIAA
	NE	↓	–	↓	↑	↑
	DA	–	–	–	–	–
	Epi	–	–	–	↑	–
50%	5-HT	remained ↓	↑	remained ↓	↑ 5-HTP	–
	NE	remained ↓	–	↑ return	↓ return	↓ return
	DA	–	↑	–	–	–
	Epi	–	–	–	↓ return	↓
Exhaustion	5-HT	↑ return	↓ return	↑ return	–	–
	NE	↑ return	–	↑↑ return	–	–
	DA	–	↓ return	–	–	–
	Epi	–	↓	–	–	↑ return

Arrows indicate significant increases (↑) or decreases (↓) in central monoamine concentration ('–' indicates no change) compared with isolated controls. As treatments were sequential, the comment "remained ↓" for animals in the 50% exhaustion group indicates that concentrations were significantly lower than controls but unchanged from stress-induced levels. The comments "↑ return" or "↓ return" in the 50% or complete exhaustion groups indicates that monoamine concentrations returned to control levels following a decrease or increase caused by the previous treatment. All serotonergic measures are from Emerson et al. [29]. Arrows followed by 5-HTP or 5-HIAA indicate that no change occurred in 5-HT, but there were changes in the precursor or catabolite.

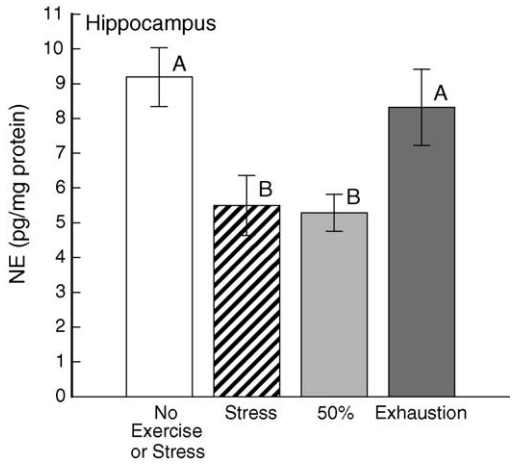

Fig. 1. Restraint stress rapidly caused a significant decrease in mean hippocampal norepinephrine (NE ± S.E.M.; levels in pg/μg protein), reversed at exhaustion. Stress was induced by holding the animal for 25 s; 50% = ½ maximal exertion time (until prodding would no longer elicit running = exhaustion). Forced physical activity followed a brief restraint stress. Groups labeled A above the bar mean are significantly different than those labeled B (Duncan's Multiple Range Test, $P < 0.05$).

area postrema. Exhaustion also reversed the effects of forced physical activity in the area postrema, and was effective in striatum.

3.1. Hippocampus

Hippocampal NE concentrations were significantly [$F_{(3,25)} = 5.62$, $P < 0.004$] reduced in animals that experienced restraint stress compared to controls (Fig. 1). This change was not affected by running to 50% exhaustion; however, at maximal exhaustion hippocampal NE returned to control levels (Table 1).

3.2. Striatum

Dopamine concentrations in striatum increased significantly [$F_{(3,23)} = 24.2$, $P < 0.0001$] with physical activity (50% exhaustion), and returned to control levels with maximal exhaustion (Fig. 2, top). Striatal DA concentrations were unaffected by restraint stress alone (Table 1).

There were no significant changes in noradrenergic parameters measured in striatum. However, striatal Epi levels, though not changed by restraint stress nor after 50% exhaustion, were significantly [$F_{(3,18)} = 7.8$, $P < 0.002$] diminished by maximal exhaustion (Fig. 2, bottom).

3.3. Locus ceruleus

In the locus ceruleus, where NE producing cells are located, the concentration of NE was significantly [$F_{(3,24)} = 5.24$, $P < 0.006$] reduced in response to restraint stress compared to controls (Fig. 3). After stress NE levels appeared to be gradually reversed by increasing exercise,

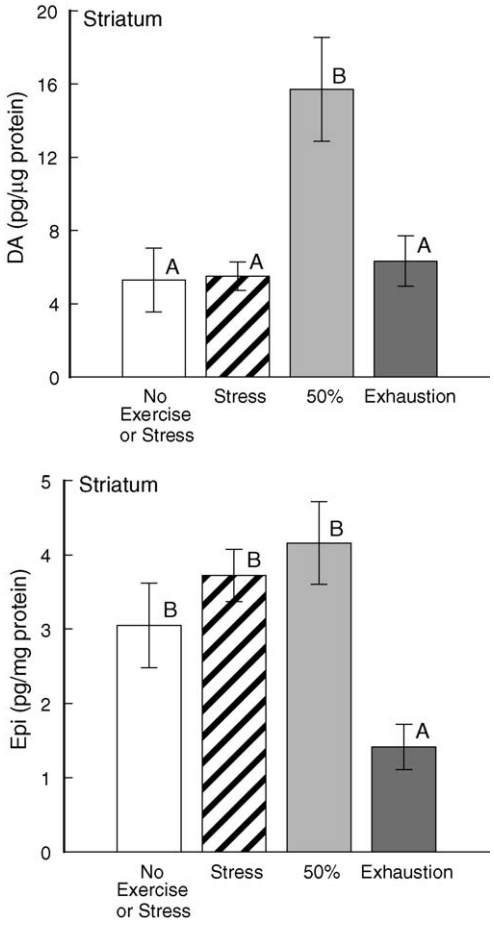

Fig. 2. Forced physical activity stimulated a significant increase in mean striatal dopamine (DA ± S.E.M.; levels in pg/μg protein), which was reversed by exhaustion. Exhaustion resulted in a reduction in striatal epinephrine (Epi). Stress was induced by holding the animal for 25 s; 50% = ½ maximal exertion time (until prodding would no longer elicit running = exhaustion). Groups labeled A above the bar mean are significantly different than those labeled B ($P < 0.05$).

such that at exhaustion NE concentrations equaled those from controls (Table 1).

3.4. Raphé

Although DA concentrations were not altered, NE concentrations in the raphé were significantly [$F_{(3,20)} = 9.06$, $P < 0.001$] increased from control levels due to restraint stress (Fig. 4, top). Any level of physical activity returned NE to control concentrations. Similarly, levels of Epi followed this same trend, being significantly [$F_{(3,19)} = 8.28$, $P < 0.001$] elevated compared to controls following stress, and returning to baseline (control levels) with exercise (Fig. 4, bottom).

3.5. Area postrema

Levels of NE in the area postrema were significantly [$F_{(3,21)} = 3.66$, $P < 0.029$] increased with restraint stress (Fig. 5, top). Subsequently, NE concentrations were reduced

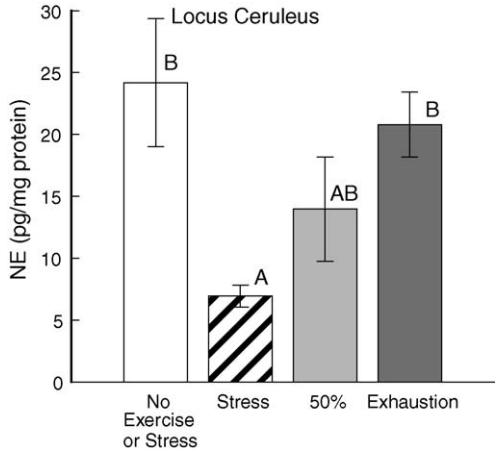

Fig. 3. Restraint stress rapidly and significantly diminished norepinephrine concentrations (NE; levels in pg/μg protein ± S.E.M.) in locus ceruleus, reversed by exhaustion. Holding the animal for 25 s was used to induce stress; 50% = ½ maximal exertion time (until prodding would no longer elicit running = exhaustion). Groups without superscript letters in common are significantly different ($P < 0.05$).

in response to any physical activity (50% exhaustion or exhaustion), returning to control levels (Table 1).

The concentration of Epi in the area postrema was significantly reduced [$F_{(3,18)} = 4.84$, $P < 0.012$] following 50% exhaustion compared to unexercised controls (Fig. 5, bottom). However, Epi levels returned to control levels with maximal exhaustion, and were unaffected by restraint stress.

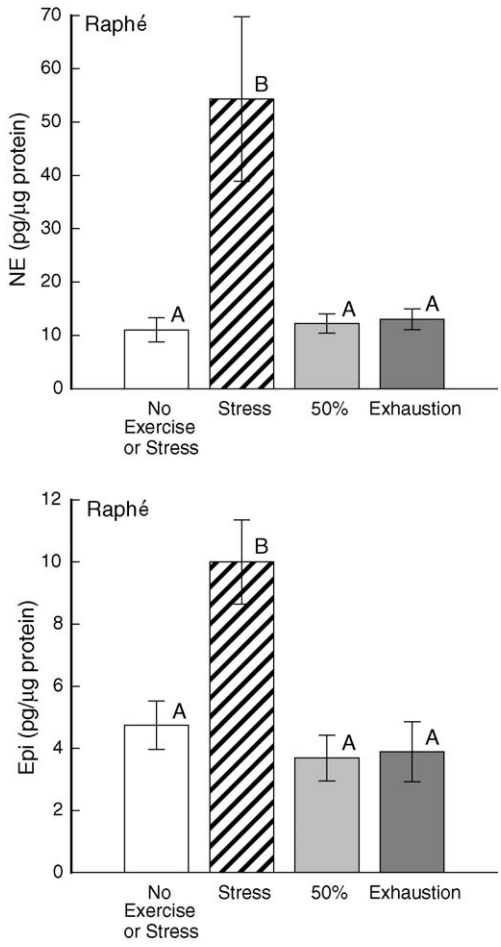

Fig. 4. Restraint stress rapidly stimulated significant elevations of norepinephrine (NE ± S.E.M.; levels in pg/μg protein) and epinephrine (Epi) in the raphé, which was reversed by forced physical activity (50%). Stress was induced by holding the animal for 25 s; 50% = ½ maximal exertion time (until prodding would no longer elicit running = exhaustion). Groups labeled A above the bar mean are significantly different than those labeled B ($P < 0.05$).

4. Discussion

Central catecholaminergic activity, like serotonergic activity [29], appears to be influenced in a region-specific manner by three interacting environmental conditions: stress, physical activity, and exhaustion (Table 1). Although the design of our experiments did not allow for comparison of stress and exercise directly (Table 1), our results do indicate that the effects of restraint stress on central catecholamine concentrations are modified by moderate forced physical activity (Figs. 4 and 5, top) and exhaustion (Figs. 1 and 3). In addition, regional catecholaminergic changes induced by forced physical activity were also sometimes reversed by exhaustion (Figs. 2, top and 4, bottom).

4.1. Stress

Restraint and/handling are relatively mild stressors that effectively stimulate secretion of plasma glucocorticoids [2,55,63,65] and catecholamines [54,66], and in addition promote elevated or depressed activity in specific brain regions of serotonergic [1,12,26,29,55] and catecholaminergic systems [1,24,61] (Figs. 1, 3–5, top). We feel fairly confident that restraint or handling is stressful, because in a series of studies restraint produced elevated plasma corticosterone, and modified central serotonergic and catecholaminergic activity [32,33,52,79]. For example, after 90 s of restraint plasma corticosterone concentrations are elevated, almost identical to elevated corticosterone measured after 90 s of social stress [77]. In our study, NE levels decreased in the hippocampus and locus ceruleus, while NE and Epi concentrations increased in the raphé following short-term restraint stress. What is more, the effects in central serotonergic [29] and catecholaminergic systems (Figs. 1, 3–5, top; Table 1) appear rather rapidly, within 25 s of the application of restraint.

Voluntary exercise has been demonstrated to promote neural and endocrine stress responses [20,69,80,81]. Although forced activity versus voluntary exercise may produce differential physiological responses [57,58], exercise of any type may necessarily be linked with stress responsiveness due to the role of glucocorticoids and their receptors in carbohydrate metabolism and therefore locomotory endurance [17]. Previously, forced physical activity has been shown to influence serotonergic systems in subiculum, medial amygdala

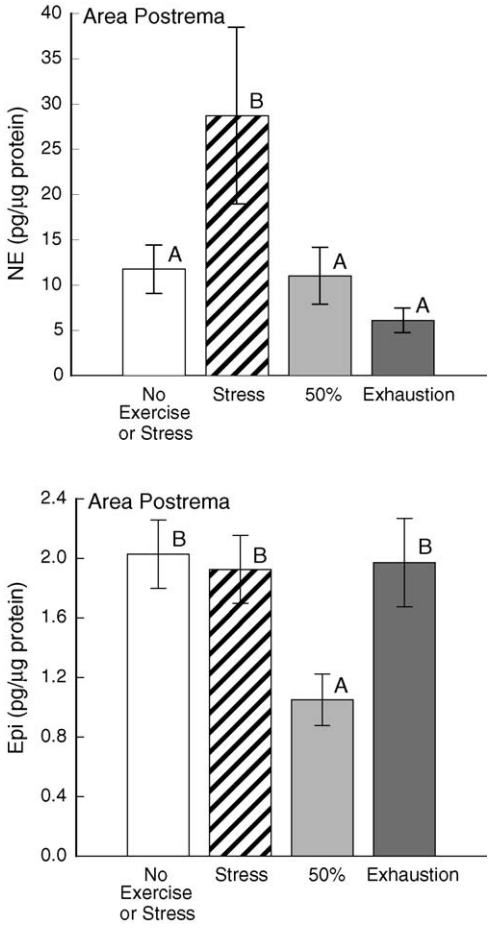

Fig. 5. Stress produced a significant rise in the concentration of norepinephrine (NE ± S.E.M.; levels in pg/µg protein) in area postrema. Epinephrine (Epi) was significantly diminished by forced physical activity (50% of maximal). Stress was induced by holding the animal for 25 s; 50% = ½ maximal exertion time (until prodding would no longer elicit running = exhaustion). Groups labeled A above the bar mean are significantly different than those labeled B ($P < 0.05$).

and raphé in *A. carolinensis* [29] and prefrontal cortex in rats [15], all of these regions are associated with stress. In our experiments, forced physical activity produced a decrease in Epi in the area postrema (Fig. 5, bottom), an area associated with stress responsiveness and osmotic/pressure balance [47,62]. While NE and Epi have been demonstrated to be widely influenced by exercise [3,6,8,10,13,25,38,56,59,64], we did not observe increased NE concentrations in the locus ceruleus, where NE is synthesized, as has been seen for both voluntary activity wheel exercise, and forced treadmill activity in rats [27]. Physical exercise paradigms have previously been demonstrated to alleviate catecholaminergic effects that are observed with other stressors such as restraint; although this phenomenon has been determined primarily by using voluntary exercise as a model of physical stress [18–21,28,46]. Stress reducing effects of forced activity in *A. carolinensis* were measured for NE in raphé and area postrema (Figs. 4, top and 5, top), and perhaps also in locus ceruleus (for which the data suggest a graded, if not significant, response with forced physical activity; Fig. 3), as well as for Epi in raphé (Fig. 4, bottom). The return of NE or Epi to control levels with exercise we suggest is an ameliorating effect of forced exercise on stress, however, it could also be simply a function of time, as the duration of physical activity (to exhaustion) lasted around 25 min, which may be sufficient time for the stress response to abate naturally. Serotonergic activity invoked by restraint stress in *A. carolinensis* is also reduced by compulsory exercise in nucleus accumbens, striatum, and area postrema [29]. Although forced physical activity is stressful [15,16,23,25,29,37], the primary effect of compulsory exercise in our experiments appears to be amelioration of the effects produced by restraint stress. The stress-ameliorating effects of forced physical activity are supported by recent studies demonstrating that forced exercise protects the brain, especially from neurodegenerative diseases like Parkinson's [67], reduces hypertension [34], and promotes longevity in rats [22].

Even more surprising than the stress ameliorating effects of forced activity, were similar results induced by exhaustion (Figs. 1 and 3; Table 1). While exhaustion must certainly be stressful, and has been demonstrated as such by promoting elevated plasma catecholamine and glucocorticoid concentrations in the lizard *Dipsosaurus dorsalis* [37], our results suggest that even locomotory activity forced to exhaustion restores restraint stress depleted NE in both hippocampus and locus ceruleus (Figs. 1 and 3). Similarly ameliorative effects of exhaustion after stress were reported for serotonergic measures in hippocampus and locus ceruleus in *A. carolinensis* [29], suggesting that in these two brain regions stress and exhaustion may be tightly linked. The overall model suggested by the amelioration of stress-induced effects due to forced physical activity and even exhaustion, is that at least for wild animals, where locomotory activity may be forced by environmental stressors such as predators or habitat loss, the forced movement may be adaptive for neuroendocrine stress responses because it marks the actual removal of the animal from stressful stimuli. The results beg the question of whether the ameliorative effects of forced physical activity on stress are evolutionarily conserved.

4.2. Physical activity—striatum

Locomotory activity increases dopaminergic function in the striatum of mammals [28,42–44,78] irrespective of whether it is forced or voluntary. Dunn and Dishman [25] reported that forced activity elicits responses that are similar to those seen with voluntary activity [25]; however, interactions with stressors were not examined [18]. In our lizards, while striatal DA did not change during restraint stress, it did increase in response to physical activity taken to 50% of exhaustion. Our results appear to extend to reptiles the association of dopaminergic activity in the striatum with movement (Fig. 2, top). This association is also suggested pharmacologically for amphibians [36], and is supported in lizards by similar changes in DA for movements associ-

ated with aggression in dominant and subordinate male *A. carolinensis* [48]. Similarly, when pharmacological application of L-DOPA (DA precursor) failed to increase DA in the striatum of *A. carolinensis*, locomotion during aggression appeared not to be affected [45]. This relationship is further strengthened by the observation that DA concentrations in the striatum are returned to baseline (control) levels by exhaustion, suggesting that DA elevated during forced physical activity is no longer stimulated when locomotion is discontinued. This contrasts with previous results by Heyes et al. [44], who found increased striatal DA at full exhaustion [44]. Locomotion associated with elevated striatal DA may be mediated by a system of balanced direct and indirect striatal GABAergic systems modulated by dopamine respectively through D_1 and D_2 receptors, as proposed by Baxter and coworkers [4,5,14].

Exhaustion alone also produced a decrease in striatal Epi (Fig. 2, bottom). This together with the result that exhaustion reversed the increase in striatal dopamine stimulated by forced activity suggests that the striatum may especially regulate both locomotion and the duration and effects of exhaustion that accrues after maximal locomotory activity has been achieved. It seems logical that one region of the brain might both control movement and reveal reduced activity when movement subsides due to exhaustion.

4.3. Locus ceruleus – raphé – monoamine cross regulation

The brainstem nuclei that produce and disperse NE (locus ceruleus), 5-HT (raphé), and DA (substantia nigra and ventral tegmental area) are reciprocally innervated, and influence each other's actions [30,31,35,41]. The results for NE and Epi in raphé (Fig. 4) and for 5-HT in locus ceruleus [29] suggest cross regulation between these transmitters for restraint stress (Table 1). A more complete picture based on monoamine modulation of social stress indicates an interregulatory relationship between NE, 5-HT, and DA [49]. Activity and production of NE in dopaminergic and serotonergic nuclei (substantia nigra, ventral tegmental area, and raphé), DA in noradrenergic and serotonergic nuclei (locus ceruleus and raphé) and 5-HT in the dopaminergic and noradrenergic nuclei (substantia nigra, ventral tegmental area, and locus ceruleus), appear to reciprocally co-vary with the monoamine produced in each of these nuclei during stress [29,49] (Fig. 4). As in the locus ceruleus, NE levels responded to restraint stress in other potentially regulatory brain regions, such as the raphé and area postrema. In addition, in each of these brain regions NE concentrations responded in the same fashion, returning to baseline (control) levels following exercise. The raphé and area postrema are terminal sites for noradrenergic neurons that originate in the locus ceruleus, similar to reciprocal innervation from serotonergic and dopaminergic perikarya, suggesting counter regulatory relationships between these monoaminergic nuclei.

5. Conclusions

Similar to the effect on serotonergic activity, brief restraint stress rapidly modifies central catecholaminergic neurotransmitters. When forced physical activity follows restraint stress in *A. carolinensis*, the effects on central monoaminergic activity were similar to those measured in mammals when voluntary physical activity followed stressful situations. That is, in the hippocampus, locus ceruleus, raphé, and area postrema changes in catecholamines induced by stress were reduced or reversed by forced exercise or exhaustion. In addition, the relationship between striatal dopamine and locomotion appear to be evolutionarily conserved, and the striatum may be important for regulating the duration and level of exhaustion as well as movement. We conclude from these observations that the effects of forced physical activity on catecholaminergic activity are context dependent, influenced by prior exposure to restraint stress.

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