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Effects of Escapable and Inescapable Foot-shock on Rat Atrial β-Adrenoceptors

ROSANA A. BASSANI[1] AND JOSÉ W. M. BASSANI

Centro de Engenharia Biomédica/Dep. Engenharia Biomédica, Faculdade de Engenharia Elétrica, Universidade Estadual de Campinas, Campinas, Sao Paulo, Brazil

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BASSANI, R. A. AND J. W. M. BASSANI. *Effects of escapable and inescapable foot-shock on rat atrial β-adrenoceptors.* PHARMACOL BIOCHEM BEHAV 44(4) 869–875, 1993.—The chronotropic responsiveness to norepinephrine (NE) and isoproterenol (ISO) was determined in right atria isolated from rats submitted to repeated escapable or inescapable foot-shock. Significant postjunctional supersensitivity to ISO, but not to NE, was observed in both groups. No significant change in the pA_2 value of metoprolol (a selective β_1-adrenoceptor antagonist) was detected. However, a decrease of the maximum response to soterenol, a partial agonist at β_1-adrenoceptors, occurred only after inescapable foot-shock. The enhanced sensitivity to ISO was abolished by butoxamine (a selective β_2-adrenoceptor antagonist) and accompanied by a marked increase in the pA_2 value of this antagonist. We conclude that the ability to control the shock prevented the down-regulation of the pacemaker β_1-adrenoceptors but not the increased participation of β_2-adrenoceptors in the response of the rat sinoatrial node to catecholamines after repeated foot-shock.

Escapable and inescapable foot-shock Stress β-Adrenoceptors Catecholamines Cardiac pacemaker

REPEATED exposure to stressful conditions has been shown to reduce both the density and the responsiveness of β-adrenoceptors to agonists in the rat brain (4,38,39,42,43). It has also been reported that the ability to escape or avoid the stressor can modify several effects brought about by the stressful treatment. Inescapable foot-shock impairs the subsequent escape response in rats (35,47,48). Compared with escapable foot-shock, it causes more marked catecholamine depletion in the CNS and more accentuated adrenocortical and analgesic responses (1,2,21,47,48).

In the rat heart, subsensitivity to the chronotropic effects of norepinephrine (NE) has been reported following repeated exposure to several stressors (8,13,20,36). Down-regulation (8,30,43) and conformational alteration of β-adrenoceptors (13,36), as well as an increase in the neuronal catecholamine uptake (8), have also been observed in hearts from stressed rats. For some stressors, such as cold (13) and foot-shock (9), subsensitivity to NE was accompanied by the induction of functional heterogeneity of the β-adrenoceptor population in the sinoatrial node.

The goal of the present study was to investigate whether the changes previously observed in atrial β-adrenergic responsiveness after repeated foot-shock are related to the lack of control of the aversive agent. Although the influence of the controllability of the stressor has been widely studied with respect to behavioral and neurochemical changes evoked by foot-shock [see (2,34,48)], this is, to our knowledge, the first report in which adrenoceptor function in a peripheral, sympathetically innervated tissue was investigated.

METHOD

Foot-shock Procedure

Adult, male Wistar rats (200–300 g) were kept in plastic cages in groups of four under controlled illumination (12 L : 12 D cycle) and temperature (22 ± 2°C) for at least 1 week before the experiments. Control (naive) rats did not experience any experimental manipulation prior to sacrifice.

The foot-shock apparatus consisted of a Plexiglas box (22 × 21 × 26 cm) with a grid floor of stainless steel rods (0.3 cm diameter). A 1-cm long lever projected into the box at a height of 5 cm from the floor. Unsignalled, 1-mA, scrambled stimuli were delivered to the grid floor from a constant-current stimulator (19). The stimulation timing was controlled by a programmable trigger (7), which received the input from a photocell circuit. This circuit responded to the sequential interruption and reestablishment of a light beam when the lever inside the box was pressed and then released, resulting in interruption of the electrical stimulus. Each foot-shock had a maximum duration of 15 s and each session consisted of 20 shocks delivered at pseudorandom intervals (60-s mean interval). Each animal was submitted to a daily session (between 8:00 and 10:00 a.m.) of either escapable or inescapable foot-shock for 3 days.

[1] Current address and address to which reprints should be sent: Department of Physiology, Loyola University Chicago, Stritch School of Medicine, 2160 1st Avenue, Maywood, IL 60153.

Escapable foot-shock. The sequential pressing and releasing of the lever by the animal during (but not before) the stimulus application was required to interrupt the shock, preventing the possibility of shock avoidance. Escape latencies for each stimulus during the three sessions were recorded from the "effective shock time" (time during which the stimulus was actually delivered to the animal) displayed by the current stimulator.

Inescapable foot-shock. In this case, the photocell circuit was disconnected from the trigger so that the shock duration could be externally controlled. The duration of each shock applied and the shock application protocol during the inescapable foot-shock session were the same for a given animal as those previously used during an escapable foot-shock session. Thus, experiments were conducted on pairs of animals, one receiving escapable foot-shock and the other being submitted to the same temporal stimulation under inescapable condition. This experimental design was chosen to minimize differences between the two groups (e.g., total foot-shock time, foot-shock presentation).

Pharmacological Procedure

Immediately after the last foot-shock session, animals were sacrificed by cerebral concussion and section of cervical blood vessels. The right atrium was isolated from the heart and mounted for isometric recording of the spontaneous contractions in a 20-ml organ bath containing Krebs-Henseleit solution with the following composition (mM): NaCl 115, KCl 4.6, $CaCl_2$ 2.5, KH_2PO_4 1.2, $NaHCO_3$ 25, $MgSO_4$ 1.2, glucose 11.1, pH 7.4. The solution was maintained at 36°C and continuously gassed with 95% O_2, 5% CO_2. The preparation was equilibrated for 45 min to allow stabilization of the spontaneous beating rate.

In vitro pretreatments. a) Adrenergic denervation by exposure to 12 μM 6-hydroxydopamine for 15 min, using 15 μM glutathione as antioxidant (3); b) treatment with 10 μM phenoxybenzamine for 15 min to irreversibly block α-adrenoceptors (16), muscarinic cholinergic receptors (18), and extraneuronal catecholamine uptake ($uptake_2$) (23); c) when NE was used, neuronal catecholamine uptake ($uptake_1$) was inhibited by continuous incubation with 0.1 μM imipramine (44). Preliminary experiments revealed that similar effects were obtained using either 6 μM cocaine or imipramine in this concentration.

Concentration-effect curves to agonists. After the stabilization period or in vitro pretreatment, cumulative concentration-effect curves (CECs) to the positive chronotropic effects of catecholamines [NE and isoproterenol (ISO)], soterenol (SOT), or theophylline (THEO) were determined. The sensitivity of the preparation to the agonists was evaluated by the pD_2 values (negative logarithm of the molar concentration of the agonist that produces a response that is 50% of the maximum response).

pA_2 values of antagonists. The participation of the β-1 and β-2 subtypes in the mediation of the chronotropic response to a nonselective β-adrenoceptor agonist was analyzed by determination of the pA_2 values of subtype-selective competitive antagonists. This method has been widely used for receptor classification [for review, see (17,26)]. The pA_2 value is defined as the negative logarithm of the molar concentration of the antagonist required to cause a twofold increase in the agonist concentration necessary to produce a given response. In homogeneous receptor populations, this value does not depend upon the selectivity of the agonist employed and is an estimate of the pK_B (negative logarithm of the apparent dissociation constant of the antagonist at the receptors). Theoretically, different receptor populations may yield different pA_2 values for the same subtype-selective antagonist.

The pA_2 values of metoprolol (MET) and butoxamine (BUT) were determined according to Arunlakshana and Schild (6), using ISO as the agonist. After in vitro pretreatment, CECs to ISO in the absence and in the presence of different antagonist concentrations (15–300 nM for MET and 1–30 μM for BUT) were obtained. The ratio of the equieffective concentrations (dr) was calculated from the ISO pD_2 values in the absence and presence of the antagonist. The Schild plot was determined for the relationship between log (dr-1) and the molar concentrations of the antagonist. For straight lines with slopes not statistically different from 1.0, pA_2 was considered as the *x*-axis intercept, according to the equation:

$$pA_2 = \log (dr - 1) - \log [B]$$

where [*B*] represents the antagonist molar concentration.

When CECs were determined in the presence of competitive antagonists, atria were previously incubated with the antagonist for 45–60 min to allow equilibration.

Chemicals

The drugs employed in this study were: BUT HCl (Burroughs-Wellcome, Research Triangle Park, NC), glutathione (Sigma Chemical Co., St. Louis, MO), 6-hydroxydopamine HBr (Sigma), imipramine HCl (Sigma), (±)-ISO sulfate (Sigma), (±)-MET tartrate (Wellcome), (−)-NE bitartrate (Sigma), phenoxybenzamine, free base (Smith, Kline & French, Philadelphia, PA), SOT HCl (Bristol-Myers, Syracuse, NY), and THEO (Sigma).

Work solutions were kept on ice and prepared daily from aliquots of stock solutions stored at −20°C. All drugs were dissolved in bidistilled, deionized water except for phenoxybenzamine, which was dissolved in absolute ethanol. ISO, NE, and 6-hydroxydopamine stock solutions also contained ascorbic acid (50 mg/ml).

Statistical Analysis

Comparison among groups was done by one- or two-way analysis of variance (ANOVA) followed by posthoc *t*-test (37). Values of p equal to or less than 0.05 were considered statistically significant. Schild plots were calculated by the least squares method. The Schild plot slopes are presented with the respective confidence intervals (41).

RESULTS

Animals submitted to escapable shock showed progressively shorter escape latencies both as the shock session proceeded and in subsequent sessions ($p < 0.05$; $df = 3$; 228 and 2; 228, two-way ANOVA). For example, the average latency for the first five trials in the first session was 6.04 ± 0.64 s, but it decreased to 3.24 ± 0.76 s for the last five trials in the third session ($n = 20$). This result confirms the acquisition of the escape behavior and implies that, during the sessions, the total effective shock time for both groups [escapable (ESC) and inescapable (INS)] was progressively reduced.

Sensitivity of Right Atria to Agonists

Repeated exposure to foot-shock did not affect the resting spontaneous rate of the isolated right atria (control, 290 ± 4

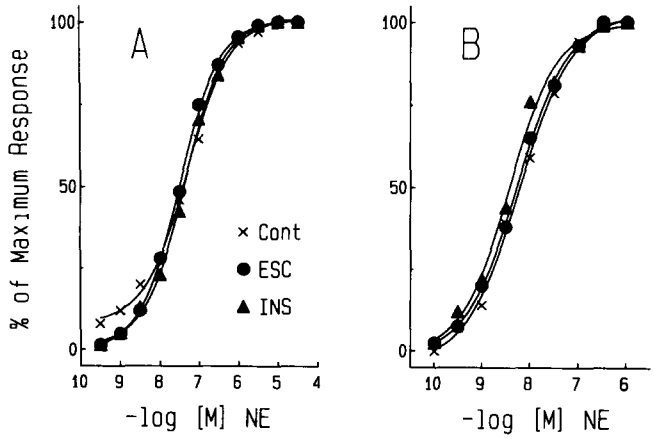

FIG. 1. Chronotropic effect of norepinephrine (NE) in right atria isolated from control (Cont) rats and after repeated escapable (ESC) and inescapable (INS) foot-shock. A, experiments performed without any in vitro pretreatment; B, curves were obtained in the presence of 0.1 μM imipramine, after adrenergic denervation with 12 μM 6-hydroxydopamine and treatment with 10 μM phenoxybenzamine. Pooled data are presented (see Table 1).

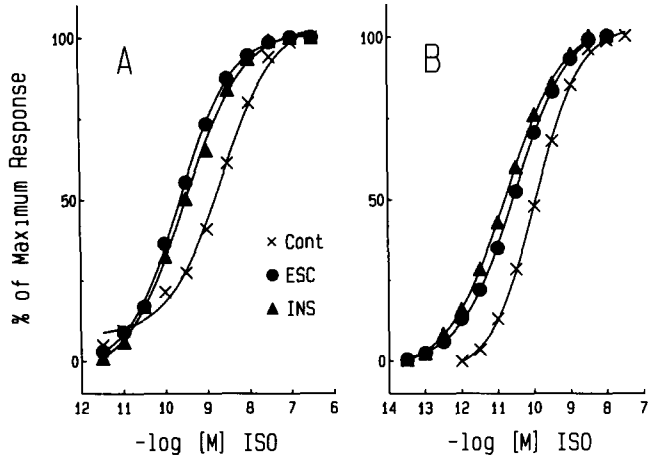

FIG. 2. Chronotropic effect of isoproterenol (ISO) in right atria isolated from control (Cont) rats and after repeated escapable (ESC) and inescapable (INS) foot-shock. A, experiments performed without any in vitro pretreatment; B, atria were pretreated in vitro with 12 μM 6-hydroxydopamine and 10 μM phenoxybenzamine. Pooled data are presented (see Table 2).

beats/min; ESC, 290 ± 3 beats/min; INS, 288 ± 3 beats/min, n = 47).

Figure 1 and Table 1 show that foot-shock did not significantly affect the chronotropic response of the right atria to NE. In vitro adrenergic denervation and blocking of uptake$_1$ shifted the CEC to NE to the left by approximately the same extent in control (6.6 times) and ESC (6.3 times) groups. In INS, the shift was greater (10.2 times), although the difference among groups was not statistically significant.

However, with ISO as the agonist preparations from foot-shock-stressed rats displayed significantly higher pD_2 values ($p < 0.01$), which clearly characterized supersensitivity in these preparations (see Fig. 2A and Table 2). This change remained even in denervated preparations, in which uptake$_2$ had been irreversibly inhibited (Fig. 2B). On the other hand, when in vitro pretreated atria were exposed to 1 μM BUT during the CEC to ISO a significant ($p < 0.01$) rightward shift of the ISO CEC was observed only in atria from foot-shock-exposed rats. The sensitivity to ISO was not affected by BUT in control preparations (see Table 2). Thus, BUT, a selective, competitive β_2-antagonist, was able to abolish the foot-shock-induced supersensitivity to ISO. In all cases, the pD_2 values of ISO observed in ESC were not different from those in INS.

TABLE 1

CHRONOTROPIC EFFECT OF NE IN RIGHT ATRIA ISOLATED FROM CONTROL (CONT) RATS AND RATS SUBMITTED TO ESCAPABLE (ESC) AND INESCAPABLE (INS) FOOTSHOCK FOR 3 DAYS

Group	n	pD_2	Maximum Response (beats/min)
Cont	6	7.42 ± 0.06	120 ± 26
ESC	6	7.49 ± 0.14	165 ± 22
INS	6	7.37 ± 0.09	170 ± 26
Cont PT	5	8.24 ± 0.08	105 ± 42
ESC PT	6	8.29 ± 0.13	135 ± 24
INS PT	6	8.38 ± 0.11	150 ± 19

PT, experiments carried out in the presence of 0.1 μM imipramine after pretreatment with 12 μM 6-hydroxydopamine and 10 μM phenoxybenzamine. Values are expressed as means ± SEM. All pD_2 values in PT are significantly different ($p < 0.01$) from nonpretreated preparations.

TABLE 2

CHRONOTROPIC EFFECT OF ISO IN RIGHT ATRIA ISOLATED FROM CONTROL (CONT) RATS AND RATS SUBMITTED TO ESCAPABLE (ESC) AND INESCAPABLE (INS) FOOTSHOCK FOR 3 DAYS

Group	n	pD_2	Maximum Response (beats/min)
Cont	6	8.79 ± 0.17	120 ± 24
ESC	6	9.62 ± 0.14*	160 ± 24
INS	6	9.53 ± 0.13*	165 ± 28
Cont PT	12	9.48 ± 0.11	150 ± 21
ESC PT	11	10.12 ± 0.19*	150 ± 18
INS PT	6	10.34 ± 0.21*	145 ± 16
Cont PT + BUT	6	9.37 ± 0.17	170 ± 26
ESC PT+ BUT	6	9.20 ± 0.11†	160 ± 26
INS PT + BUT	6	9.20 ± 0.13†	165 ± 22

PT, experiments carried out after pretreatment with 12 μM 6-hydroxydopamine and 10 μM phenoxybenzamine; BUT, experiments conducted on pretreated preparations in the presence of 1 μM butoxamine. Values are expressed as means ± SEM. All pD_2 values in PT are significantly different ($p < 0.05$) from nonpretreated preparations.

*Significantly ($p < 0.01$) different from control.

†Significantly ($p < 0.01$) different from same group in the absence of buoxamine.

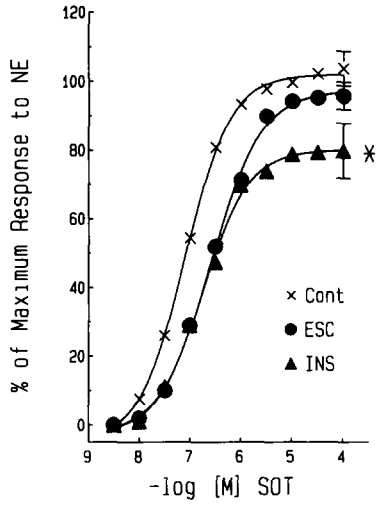

FIG. 3. Concentration effects curve to soterenol (SOT) in right atria isolated from control (Cont) rats and after escapable (ESC) and inescapable (INS) foot-shock. Response to SOT is expressed as a percentage of the maximum response to norepinephrine (NE). Bars represent SEM (points represent the mean of four to eight experiments). Data are means. SEM is presented for maximum response only. *Significantly different ($p < 0.01$) from control.

Figure 3 shows CECs to SOT, a partial agonist at β_1-adrenoceptors, in atria from control and foot-shock-stressed rats. No significant difference among the groups was found regarding to the pD_2 values (control, 7.01 ± 0.11, $n = 8$; ESC, 6.68 ± 0.09, $n = 4$; INS, 6.76 ± 0.08, $n = 8$). However, when comparing the maximum chronotropic response to this agonist as a percentage of the maximum response to a full agonist (NE) at the same receptor subtype we observed a significant ($p < 0.01$) decrease only in the INS group, while the maximum response to SOT did not differ between control and the ESC group (control, 104 ± 5%; ESC, 96 ± 4%; INS, 80 ± 8%).

TABLE 3

pA_2 VALUES AND SLOPES OF SCHILD PLOTS FOR METROPROLOL (MET) AND BUTOXAMINE (BUT) IN RIGHT ATRIA ISOLATED FROM CONTROL (CONT) RATS AND RATS SUBMITTED TO ESCAPABLE (ESC) AND INESCAPABLE (INS) FOOTSHOCK FOR 3 DAYS

Group	n	pA_2	Slope
MET			
Cont	9	8.32 ± 0.07	0.98 (0.80–1.16)
ESC	12	8.30 ± 0.11	0.90 (0.71–1.09)
INS	12	8.49 ± 0.10	0.93 (0.74–1.11)
BUT			
Cont	11	5.43 ± 0.07	1.13 (0.96–1.30)
ESC	12	6.31 ± 0.05*	1.04 (0.95–1.14)
INS	10	6.73 ± 0.10*	0.86 (0.71–1.01)

pA_2 values are expressed as means ± SEM. Slopes are presented as means (95% confidence interval).

*Significantly ($p < 0.01$) different from control.

CECs to THEO (an agonist that bypasses β-adrenoceptors) did not reveal any significant difference in either the pD_2 values (control, 3.87 ± 0.06; ESC, 3.67 ± 0.09; INS, 3.61 ± 0.09) or maximum response (control, 135 ± 19 beats/min; ESC, 120 ± 31 beats/min; INS, 125 ± 12 beats/min; $n = 6$ in each group).

Antagonist pA_2 Values

Table 3 shows the slopes and pA_2 values from Schild plots determined for two subtype-selective competitive antagonists: MET (β_1) and BUT (β_2). The respective Schild plots are illustrated in Figs. 4A and 4B, respectively.

Foot-shock did not significantly change the pA_2 of MET. Although the slope of the regression line did not statistically differ from 1.0, it can be seen in Fig. 4A that the monotonic increase of log (dr-1) with increasing [B] was interrupted for 0.3 μM MET in the foot-shock-exposed groups only (circles and triangles in Fig. 4A). This could be interpreted as a trend of the slope of the Schild plot to depart from 1.0.

On the other hand, the analysis of the ability of BUT to antagonize the effects of ISO revealed a dramatic (approximately 1 log unit, $p < 0.01$) increase of its pA_2 in atria isolated from foot-shock-stressed rats, both ESC and INS (see Table 3 and Fig. 4B). The Schild plot slopes did not differ significantly from 1.0.

DISCUSSION

The present results show that both escapable and inescapable foot-shock (repeated for 3 days) caused supersensitivity to the chronotropic effects of ISO without significantly affecting the responsiveness to NE in the isolated rat right atrium. This change could be abolished in vitro by BUT, a β_2-adrenoceptor selective antagonist, and was probably due to the appearance of a functionally active subpopulation of β_2-adrenoceptors because an increase of the pA_2 of BUT, but not of MET, was also observed.

Subsensitivity to NE in right atria from repeatedly stressed rats has been a common finding for a number of different stressors. After cold exposure and swimming, this change seems to arise from a conformational change of β_1-adrenoceptor (13,36). After foot-shock, however, the decreased subsensitivity to NE has been shown to have a prejunctional origin, probably caused by enhanced activity of uptake$_1$ because it was

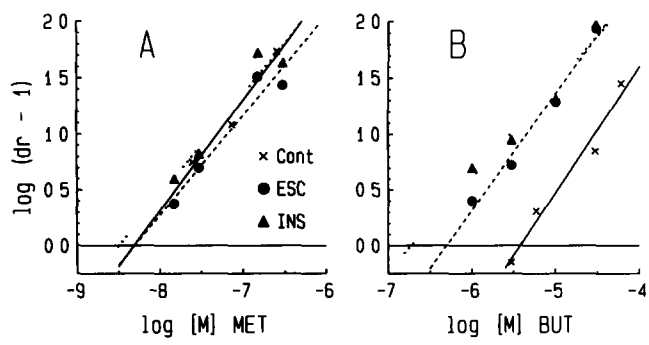

FIG. 4. Schild plots for metoprolol (MET, A) and butoxamine (BUT, B) in right atria isolated from control (Cont) rats and rats submitted to escapable (ESC) and inescapable (INS) foot-shock. Points represent the mean of at least four experiments.

reversed by cocaine (8). The failure of foot-shock to induce subsensitivity to NE in the present study might have been due to a decrease in the stress severity because even in the inescapable protocol the time of shock exposure was progressively decreased during the sessions. However, we observed a trend of increased effectiveness of imipramine to shift the CEC to NE to the left after inescapable foot-shock. Absence of qualitative change in β_1-adrenoceptor function in both foot-shock groups was suggested by the lack of significant alteration of the NE sensitivity in in vitro pretreated atria and of the pA_2 of MET, as previously observed (8,9). A change in postreceptor mechanisms was also unlikely because atria from foot-shock-stressed rats responded to THEO in a similar way to control preparations [THEO increases intracellular cyclic adenosine monophosphate levels by inhibition of its degradation by phosphodiesterases; see (12)].

An important difference between ESC and INS was that the maximum response to SOT was decreased in atria from the latter group alone. SOT is a partial agonist at β_1-adrenoceptors, having coincident occupation and concentration–effect curves for the chronotropic response to catecholamines in the isolated rat right atrium (11). This indicates absence of spare receptors for this agonist in the atrial preparation. Thus, the maximum response would occur only after occupation of all available receptors, and changes in receptor density would be reflected by corresponding changes in the maximum response to the partial agonist. Accordingly, changes in the maximum response to partial agonists (with no changes in the pD_2 value, i.e., no change in apparent affinity) have been shown to parallel changes in the density of receptor binding sites (27). This shows that partial agonists may be useful for detection of alterations of receptor density, although this approach does not allow quantification of such changes. Thus, our results confirm those previously reported showing that β-adrenoceptors are downregulated in rat hearts after repeated, inescapable stress (8,30,43). Moreover, they indicate that this change does not occur when the animal can control the stressor, even when receiving the same total time of shock. Down-regulation of cardiac β-adrenoceptors during stress has been attributed to increased catecholamine release (43). It has also been reported that the foot-shock-induced catecholamine depletion in the rat hypothalamus is less severe in the controllable condition (47,48). If during foot-shock changes in catecholamine release in the heart parallel those occurring in the hypothalamus, as demonstrated for other stressors (32), it could be expected that during inescapable shock a more massive release would occur, thus causing down-regulation of atrial β_1-adrenoceptors. However, this alteration was not severe enough to depress the responses to NE or ISO, which can produce 50% of the maximum response with a fractional occupation of less than 5% of the β-adrenoceptors in rat right atria (11).

On the other hand, the ability to escape from shock did not prevent the appearance of a postjunctional supersensitivity to ISO in the right atrium. A prejunctional origin for this change could be discarded because it was present even after in vitro adrenergic denervation (see Table 2). Because supersensitivity was observed to ISO (a nonsubtype-selective β-adrenoceptor agonist) but not to NE [which is selective for the β_1-subtype; see (28,29)], we investigated the role of postjunctional β_2-adrenoceptors in this alteration. We observed that BUT, a selective β_2-adrenoceptor antagonist, was able to suppress this change in atria from foot-shock-stressed animals without interfering with the ISO sensitivity in control preparations. These findings suggest that this alteration is due to increased activation of β_2-adrenoceptors. Indeed, the Schild plot for BUT revealed that foot-shock increased the pA_2 of this antagonist by one order of magnitude. In control atria, the pA_2 of BUT was close to that determined in guinea pig right atria, where the chronotropic response to catecholamines is predominantly mediated by the β_1-subtype. In atria from stressed rats, however, the pA_2 value was similar to that obtained in guinea pig trachea, where catecholamine-mediated relaxation is mediated mainly by the β_2-subtype (22).

The β_2-adrenoceptor subtype comprises 30 and 50% of the total β-adrenoceptor population in rat atrial (24) and sinus nodal tissues (33), respectively. However, in the rat the participation of these receptors in the mediation of the positive chronotropic effect of catecholamines is undetectable or very small (24,25,31). Indeed, we previously observed that incubation with BUT affects neither the sensitivity of control rat right atria to ISO and epinephrine nor the pA_2 of MET (9). However, after foot-shock exposure BUT can prevent both supersensitivity to these agonists and the change in the pA_2 value of MET [(9), present results]. Also, the role of β_2-adrenoceptors in this phenomenon was evidenced by the finding that atria from foot-shock-stressed rats were also supersensitive to salbutamol, a selective β_2-adrenoceptor agonist (9). Together, these results suggest that repeated foot-shock increases the participation of atrial pacemaker β_2-adrenoceptors to catecholamines, including epinephrine, the main sympathetic neurohormone. Moreover, this change is not caused by the inability to control the stressor because it takes place also after escapable foot-shock.

The cellular mechanisms underlying this phenomenon are still not clear. However, the increase in the β_2-adrenoceptor function after foot-shock does not seem to involve simultaneous downregulation of the β_1-subtype, as it happens in the failing human heart (10), because after escapable shock we could detect only the former. The onset of atrial supersensitivity to ISO and epinephrine after repeated foot-shock in the rat requires corticosterone (S. De Moraes, personal communication). It is well known that glucocorticoids can induce the synthesis of β_2-adrenoceptors (14). Thus, elevated plasma levels of glucocorticoids during foot-shock might have induced β_2-adrenoceptor synthesis in the rat sinus node. Alternatively, these hormones might have increased the coupling efficiency of preexistent and/or newly synthesized receptors to adenylate-cyclase, as described in guinea pig trachea after cortisol treatment (15).

Although Weiss et al. (47) reported that the magnitude of the adrenocortical response after controllable foot-shock was smaller than after uncontrollable shock in rats, some authors (21,34) did not observe differences in the increase of plasma corticosterone in these conditions. On the other hand, it has been shown that the hormonal adrenocortical response is essential for the maintenance of the escape behavior in rats (40) and is slowly decreased as the escape behavior is acquired (45). Thus, it is possible that the appearance of functional β_2-adrenoceptor in the atrial pacemaker of the rat, with consequent increased sensitivity to epinephrine (9), reflects an adaptative process rather than a pathologic consequence of the stress.

It is in general accepted that in basal conditions the sympathetic modulation of cardiac function is predominantly neural, mediated through NE release from the adrenergic nerve terminals. During stress, however, there is an increase in the participation of the humoral component (represented by circu-

lating epinephrine), which is minimal in basal conditions (5). The enhancement of cardiac β_2-adrenoceptor function during repeated stress might magnify the role of epinephrine as a chemical modulator of the heart rate because epinephrine, differently from NE, does not discriminate between β-adrenoceptor subtypes (28,29). Considering that depletion of cardiac NE content has been observed during exposition of rats to several stressors (46), the increase of cardiac responsiveness to epinephrine would be important in the maintenance of the sympathetic modulatory influence on the heart during stress.

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