Sympathetic and angiotensin-dependent hypertension during cage-switch stress in mice

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Lee, Dexter L., R. Clinton Webb, and Michael W. Brands. Sympathetic and angiotensin-dependent hypertension during cage-switch stress in mice. Am J Physiol Regul Integr Comp Physiol 287: R1394–R1398, 2004. First published August 12, 2004; doi:10.1152/ajpregu.00306.2004.—The goal of this study was to determine the dependence of the acute hypertensive response to a novel model of acute psychosocial stress on the sympathetic and renin-angiotensin systems. Baseline mean arterial pressure (MAP), heart rate (HR), and locomotor activity were measured with telemetry in mice for a 1-h period and averaged 98 ± 1 mmHg, 505 ± 3 beats/min, and 5 ± 1 counts, respectively. Stress was induced by placing a mouse into a cage previously occupied by a different male mouse, and this increased MAP, HR, and activity in the control group by 40 ± 2 mmHg, 204 ± 25 beats/min, and 68 ± 6 counts, respectively. Each variable gradually returned to baseline levels by 90 min after beginning cage switch. Pretreatment with terazosin (10 mg/kg ip) significantly reduced the initial increase in MAP to 12 ± 6 mmHg, whereas MAP for the last 45 min was superimposable on control values. Atenolol (10 mg/ml drinking water) had no effect to blunt the initial increase in MAP but had a growing effect from 10 min onward, decreasing MAP all the way to baseline by 60 min after starting cage switch. Captopril (2 mg/ml drinking water) treatment caused a very similar response. All three treatments significantly decreased the area under the blood pressure curve, and the blood pressure effect could not be attributed uniformly to effects on HR or activity. These data suggest that our novel model of psychosocial stress causes an initial α₁-receptor-dependent increase in MAP. The later phase of the pressor response is blocked similarly by a β₁-receptor antagonist and an ACE inhibitor, independent of HR, suggesting that the β₁-dependent blood pressure effect is due, in large part, to the renin-angiotensin system.

mean arterial pressure; sympathetic nervous system; renin-angiotensin system

PSYCHOSOCIAL STRESS INCREASES arterial pressure and also has been linked to chronic renal and cardiovascular disease, including hypertension (1, 9, 17, 19). Stress causes activation of the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenocortical axis, with responses that include increases in body temperature, blood pressure, heart rate (HR), and plasma glucocorticoid concentration. Interference with either system compromises the body’s ability to respond to the stressors (2, 16, 20). The well-described effects of the SNS are mediated through α₁- and β₁-adrenergic receptors located on the heart and throughout the vascular system, which includes the stimulation of renin secretion and subsequent increase in ANG II production (3, 4, 7, 8, 10, 18).

We have a new experimental model of psychosocial stress that is caused by placing a male mouse in a cage previously occupied by another male mouse. Termed cage switch (CS), this is a modification of earlier models of stress, in which rats or mice are switched to a clean cage or a cage with a layer of water at the bottom (12–15, 21). The hypertension in those models is ~20 mmHg, but reproducible, and the unique feature of our CS model is that it capitalizes on that reproducibility and combines the more robust hypertension characteristic of psychosocial stress (~40 mmHg) but without complex caging paradigms or fighting. The pressor response is reproducible, takes over 90 min to subside, and is accompanied by significant increases in HR and motor activity. The goal of this study was to determine the roles of α₁- and β₁-adrenergic receptors in mediating these responses to stress in this new model. In addition, the effects of α₁ and β-blockade led us to test the hypothesis that ANG II also played a significant role in the rapid hypertensive response to stress in this model.

METHODS

Animals. Procedures involving animals were approved by the Animal Care and Use Committee of the Medical College of Georgia and complied fully with those approved by the American Veterinary Medical Association Panel on Euthanasia. Surgery was performed on male C57BL/6J (Jackson Laboratories C57BL/6J 000664) mice (6 to 8 wk of age) to implant a blood pressure transmitter (Data Science, PA-C20). Briefly, the mice were anesthetized with isoflurane at 2–3% in a stream of 100% oxygen mixed with room air. A Data Sciences transmitter catheter was inserted into the left carotid artery via a 10-mm incision on the ventral neck region over the trachea, and the transmitter body was routed to a subcutaneous pocket in the mid-scapular region. The incision was closed with sterile, 6–0 Ethicon Ophthalmic suture. After recovery, mice were housed in individual cages in the laboratory animal facilities with a 12:12-h dark-light cycle and provided with standard laboratory chow and water ad libitum. Because CS experiments were conducted from 1000 to 1500 h, baseline mean arterial pressure (MAP) was measured 19 h/day, from 1500 to 1000 h the next day. CS experiments were not begun until normal circadian rhythm was reestablished (~4–7 days postsurgery).

Stress. All mice were placed in a clean cage for 3 days before CS stress. On the day of the study, the mice were observed for 120 min in their home cages, undisturbed from the room in which they were housed before testing. These were the last 2 h of the 19-h measurement period (i.e., from 0800 to 1000 h). The CS then was begun at 1000 h by removing mice from their original cage and placing them randomly into a cage previously occupied by a different male mouse for a period of 5 h. Because we could not measure consistent effects of any treatment on the blood pressure response to stress after ~90 min, only the first 90 min following CS were analyzed for peak and area under the curve (AUC) responses.

Sham CS. As a control for handling, mice in a separate group (n = 5) were picked up and placed back in their own cage.

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Experimental groups. Terazosin (α1-receptor antagonist) group (n = 5): terazosin (10 mg/kg) was administered via an intraperitoneal injection 3 h before CS stress. Atenolol (β1-receptor antagonist) group (n = 6): atenolol (10 mg/ml) was administered in the drinking water beginning 7 days before CS stress. Captopril (angiotensin-converting enzyme inhibitor) group (n = 5): captopril (2 mg/ml) was administered in the drinking water beginning 7 days before CS stress. Mice that were treated with terazosin were given a period of 2 wk for a washout period before being treated with atenolol. Likewise, mice that were treated with atenolol were given a period of 2 wk before being treated with captopril. In each case, MAP, HR, and locomotor activity returned to pretreatment levels before starting atenolol or captopril. In each case, MAP, HR, and locomotor activity returned to pretreatment levels before starting atenolol or captopril. 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significantly different from control: 1,097 ± 115, 4,725 ± 1,293, and 1,538 ± 436 mmHg/min, respectively.

In the atenolol-treated groups, after 7 days of atenolol in the drinking water, baseline MAP, HR, and motor activity before CS stress were 98 ± 1 mmHg, 417 ± 3 beats/min, and 8 ± 1 counts, respectively, and the HR was significantly less than that of control animals. The peak change in MAP during CS stress was 37 ± 3 mmHg. The peak changes in HR and motor activity were 148 ± 20 beats/min and 43 ± 4 counts, respectively, and were significantly different from control (Fig. 2). The AUC for the MAP was significantly decreased in animals treated with atenolol (796 ± 163 mmHg/min) compared with controls (914 ± 141 mmHg/min). The AUCs for HR and locomotor activity were not significantly different from control: 7,863 ± 1,351 and 2,178 ± 346 mmHg/min, respectively (Fig. 4).

When the sham switch mice were picked up and returned to their own cage, the average peak changes for MAP, HR, and motor activity were 22 ± 5 mmHg, 122 ± 9 beats/min, and 31 ± 5 counts, respectively. These all were significantly less than the control group CS response, and the time for return to control also was less. The AUC is shown in Fig. 4.

DISCUSSION

This study provided evidence that the rapid, peak increase in MAP following onset of psychosocial stress is due, to a significant extent, to α-adrenergic mechanisms, whereas β-adrenergic mechanisms played a quantitatively greater role be-
The control group. It also was interesting that locomotor activ-

ation after starting CS, compared with 40 mmHg at 1–3 min in

terazosin treatment was only 20 mmHg and it occurred 10–20

min. The captopril data supported this hypothesis by showing an

attenuated increase in MAP during stress that was almost an

identical response to that in the atenolol-treated group. Captopril

treatment had no effect on the HR or blood pressure responses.

Thus, even though we did not measure renin secretion, these effects of β1-receptor blockade and inhibition of angiotensin-converting enzyme provide strong evidence that ANG II played an important role in the acute hypertensive response. Previous studies suggested a role for ANG II in acute stress-induced increases in blood pressure (3, 10, 18); however, the findings are not universal. Moreover, it is not known to what extent the blood pressure response is due to peripheral actions or to central actions to modulate SNS activity. Our data do not provide insight into this aspect of the response, but they do provide strong evidence that in this unique model of psychosocial stress, ANG II plays a major role in the blood pressure response.

This study, therefore, describes a new model of acute psychosocial stress caused by placing male mice into cages that have been occupied previously by different male mice. The increase in telemetry-measured MAP followed by CS stress is ~40 mmHg and it is accompanied by significant increases in HR and motor activity. This robust hypertensive response can be broken into a rapid α1-receptor-dependent phase and a sustained β1-receptor-dependent phase, and the β1-effect on blood pressure appears to be independent of increased HR and due almost exclusively to control of the renin-angiotensin system. Further studies that quantify renin secretion, during control and atenolol treatment conditions, and the role of central vs. peripheral actions of ANG II will be needed to better delineate these relationships.

GRANTS

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REFERENCES


