Hemodynamic response patterns to acute behavioral stressors resemble those to cocaine

MARK M. KNUEPFER, ROBERT M. PURCELL, QI GAN, AND KHOI M. LE
Department of Pharmacological and Physiological Science, St. Louis University
School of Medicine, St. Louis, Missouri 63104

Received 4 June 2001; accepted in final form 2 August 2001

Knuepfer, Mark M., Robert M. Purcell, Qi Gan, and Khoi M. Le. Hemodynamic response patterns to acute behavioral stressors resemble those to cocaine. Am J Physiol Regulatory Integrative Comp Physiol 281: R1778–R1786, 2001.—Hemodynamic responses to cocaine vary greatly between animals, and the variability is related to the incidence of cocaine-induced cardiomyopathies and hypertension. The variability in cardiac output and systemic vascular resistance responses to cocaine in individuals is correlated with the responses to acute startle (air jet). This experiment was designed to determine whether responses to cocaine and to air jet are related to those evoked by a conditioned stimulus (tone preceding foot shock) and to an unconditioned stimulus (cold water). We verified the relationship in hemodynamic response patterns between cocaine and cold stress using selective receptor antagonists. Rats were instrumented with a pulsed Doppler flow probe on the ascending aorta for determination of cardiac output and with an arterial cannula for recording arterial pressure and heart rate. After recovery, some rats were tested multiple times with four different stimuli: air jet (6 trials), 15-s tone preceding 1-s foot shock (12 trials), cold water exposure (1 cm deep for 1 min, 4–12 trials), and cocaine (5 mg/kg iv, 4–6 trials) while hemodynamic parameters were recorded. Each stimulus was capable of eliciting a pressor response that was associated with variable changes in cardiac output. The cardiac output response to cocaine was correlated with the initial responses to each stressor in individual rats. Responses evoked by cold stress were most similar to those elicited by cocaine. Furthermore, nicardipine (25 μg/kg iv) or atropine methyl bromide (0.5 mg/kg iv) pretreatment prevented the cardiac output differences to acute cold stress, as noted after cocaine administration. On the other hand, propranolol (1 mg/kg iv) exacerbated both the decrease in cardiac output and the stress-induced increase in systemic vascular resistance as previously reported with cocaine. Therefore, the initial response to cold water exposure is a reliable method of evoking characteristic hemodynamic response patterns that, as seen with cocaine, may provide a suitable model for identifying the causes for predilection to stress-induced cardiovascular disease.

conditioned stress; unconditioned stress; cardiac output; systemic vascular resistance; population differences

STRESS CONTRIBUTES to the susceptibility to and severity of many diseases in individuals. While it is commonly believed that stress is detrimental to one’s health, only anecdotal evidence is available suggesting that stress specifically causes cardiac disease (8, 11, 14). Although the autonomic nervous system is likely to contribute to stress-induced cardiac disease (9), the specific mechanisms by which this occurs are not understood. More importantly, clinicians may underestimate the importance of stress because they have no effective means by which to judge the ability of an individual to respond to stress appropriately. It has been suggested that cardiovascular disease may result from prolonged behavioral stress in susceptible individuals but not in all individuals (15, 37). This study is designed to establish a novel model for stress-induced hemodynamic response variability.

Certain individuals are predisposed to stress-induced cardiovascular disease presumably due to predetermined (genetically and/or learned) differences in autonomic responses to stress. Using stressful stimuli such as mental arithmetic, anxiety, and cold pressor tests, early clinical studies (6, 10) suggested that a subset of individuals had a decrease in cardiac output in response to stress, whereas the majority of subjects studied responded to stress with an increase in cardiac output despite a consistent pressor response in all individuals. Therefore, individuals with a decrease in cardiac output have greater elevations of systemic vascular resistance. Recent findings (2, 16, 19, 32, 41, 44) corroborate the differences in cardiovascular responses to stressful stimuli between individuals. Clinical studies suggest that specific autonomic response patterns to acute stress correlate with the incidence of stress-related sudden cardiac death (13, 39, 45) and hypertension (16, 41, 44). These data strongly suggest that there is considerable individual variation in functional and pathological responses of the cardiovascular system to stress in humans.

Rats also express variability in functional and pathological cardiovascular responses to cocaine. We reported that cocaine produces highly variable cardiac output responses in rats (4, 21–23). This is manifested as an increase in cardiac output in some rats and a decrease in others despite a similar elevation in arterial pressure. Inasmuch as those with a decrease in
METHODS

by cocaine and that these vary between individuals. Therefore, we propose that similar physiological mechanisms are activated by behavioral stress and cocaine. Therefore, we sought a more robust, reproducible stressor to study the causes of variable hemodynamic responses to acute stress with responses to unconditioned stress (air jet) rapidly diminished with repeated exposure, presumably due to conditioning. In contrast, hemodynamic responses to a conditioned stress (15-s tone preceding brief foot shock) were reproducible over many trials but were small in magnitude (36). As noted with repeated cocaine, repeated exposure to behavioral stress (1–3 h/day for 4 wk) produced a sustained increase in arterial pressure in vascular responders to acute stress but not mixed responders (36). These data suggest that the hemodynamic response pattern to acute stress is predictive of a predisposition to stress-induced hypertension similar to observations in humans (16, 32, 41, 44). Therefore, we sought a more robust, reproducible stressor to study the causes of variable hemodynamic response patterns to behavioral stress and their relationship to the development of hypertension.

In this study, we compared the hemodynamic response patterns to acute cold stress with responses to conditioned and unconditioned stress and to cocaine administration. The initial hemodynamic response pattern to cold stress correlated with responses to acute stress or cocaine. Furthermore, selective receptor antagonists altered hemodynamic responses to brief cold water stress in the same manner as responses to cocaine. Therefore, we propose that similar physiological mechanisms are activated by behavioral stress and by cocaine and that these vary between individuals.

METHODS

In this study, we subjected instrumented rats to acute stressors. All surgical and experimental procedures were approved by the St. Louis University Institutional Animal Care and Use Committee and followed guidelines described in the Guide for the Care and Use of Laboratory Animals (National Research Council, National Academy Press, Washington, DC, 1996).

Surgical Preparation

Specific pathogen-free, male Sprague-Dawley rats (Harlan Laboratories, Indianapolis, IN) weighing 300–370 g were used in these studies. Rats were anesthetized with pentobarbital sodium (45 mg/kg ip), intubated for artificial respiration with room air, and instrumented with a miniaturized pulsed Doppler flow probe (Iowa Doppler Products, Iowa City, IA) on the ascending aorta as described in earlier manuscripts (4, 21–26). Rats were closely monitored during the first few hours after surgery and allowed to recover for at least 1 wk.

Experimental Preparation

After 1–2 wk, rats were anesthetized with a mixture of ketamine and xylazine (55 and 7 mg/kg ip, respectively). The femoral artery and vein were exposed and cannulated for recording arterial pressure and administering drugs intravenously. Rats were allowed to recover for 2–3 days. Rats were acclimated for 6–8 h on 1 day in the test cage then for 2 h on the next day before any experiments were performed. Rats were exposed to acute air jet (20 lb/in² directed at the face from a distance of 1 cm) once every 10 min for a total of six trials while arterial pressure, heart rate (using a cardiometer), and ascending aortic blood flow were recorded on a chart recorder and digitally at 1,000 samples/s using a data-acquisition system (WINDAQ, DATAQ Instruments, Akron, OH). Subsequently, every 10 min, animals were subjected to a 15-s tone (−85 dB) followed immediately by a 1-s foot shock every 10 min for a total of 12 trials. The foot shock intensity was set to evoke a flinch but not vocalization from the rat. On the following day, rats were tested with exposure to cold water (3–5°C, 1-cm deep). Water was introduced through a large funnel and tube to the base of the cage to minimize the spread of water to areas other than the limbs of the rat. After 1 min, water was rapidly evacuated from the cage through a drain. Rats were allowed to recover at least 30 min or longer if hemodynamic values had not returned to normal. Cold stress trials were tested three to ten times with no more than four trials per day.

After characterization of rats to the three stressors, rats were given cocaine (5 mg/kg iv over 45 s). This was repeated a minimum of 4 h later. On the following day, rats were treated similarly so that at least four trials with cocaine were performed on each rat. In some rats, cold stress was repeated before and 10 min after administration of propranolol (1 mg/kg iv), atropine methylbromide (0.5 mg/kg iv), or nicardipine (25 μg/kg iv). The responses from the cold stress trial immediately before the drug administration were compared with those after drug administration.

Drugs and Chemicals

Drugs used included atropine methylbromide, nicardipine, and propranolol from Sigma Chemical (St. Louis, MO). Cocaine hydrochloride was obtained from the National Institute on Drug Abuse. Ketamine was purchased from Fort Dodge Animal Health (Fort Dodge, IA). Xylazine and pentobarbital sodium were purchased from Butler (Columbus, OH).

Data Analysis

Digitized data were analyzed using WINDAQ software (DATAQ Instruments). Hemodynamic data in all experimental paradigms were analyzed at the time of the initial peak increase in arterial pressure. These were the only data obtained for the air jet stress because the response was short-lived. The conditioned response to foot shock was recorded
within 5–10 s after the onset of the tone (the C1 response as described by Randall et al., Ref. 38). Data obtained at 15-s intervals after cold stress were analyzed. Data obtained 1, 3, and 5 min after cocaine administration were also analyzed. The initial responses to cocaine and to cold stress were used to define the phenotypic response of the animal (i.e., vascular or mixed responder).

Data were analyzed with a Student’s t-test to compare peak response data. Data obtained at multiple time points (e.g., cold stress and cocaine data or before and after drug data) were analyzed using a two-way repeated-measures analysis of variance. A P value <0.05 was considered significant. Data are expressed as means ± SE.

RESULTS

Rats (n = 38) examined in this study had a resting arterial pressure of 120 ± 2 mmHg, a heart rate of 400 ± 5 beats/min, and an ascending aortic flow of 8.7 ± 0.6 kHz shift. There were no differences in arterial pressure, heart rate, or cardiac output in resting values before presentation of stressors or cocaine (Table 1). Nineteen rats were used to compare cold stress-induced hemodynamic responses to responses to conditioned and unconditioned stress and to cocaine administration. The remaining rats (n = 19) plus 12 of the rats used for comparing responses to stressors and cocaine were used originally to determine the effects of selective antagonists.

Comparison of Hemodynamic Responses to Different Stimuli

Responses to cold stress. Rats exposed to cold water stress had an immediate pressor response that reached a peak 3–7 s after the water was introduced. At this time, some rats had increases in ascending aortic flow, whereas others had decreases. We separated rats into two groups according to whether they had an increase or a decrease in cardiac output (mixed and vascular responders, respectively) at the time of the initial pressor response. Vascular responders had significantly greater initial increases in systemic vascular resistance and decreases in cardiac output compared with mixed responders (Fig. 1).

After the initial pressor response, the hemodynamic responses to cold stress were consistent within groups (Fig. 2). Repeated exposure to cold stress (with a minimum of 30 min between trials) produced consistent responses. As

Table 1. Baseline values

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Group</th>
<th>n</th>
<th>Arterial Pressure, mmHg</th>
<th>Heart Rate, beats/min</th>
<th>Cardiac Output, kHz shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air jet</td>
<td>MR</td>
<td>6</td>
<td>122 ± 6</td>
<td>387 ± 7</td>
<td>8.1 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>VR</td>
<td>12</td>
<td>115 ± 3</td>
<td>386 ± 10</td>
<td>8.7 ± 0.4</td>
</tr>
<tr>
<td>Tone preceding shock</td>
<td>MR</td>
<td>6</td>
<td>115 ± 3</td>
<td>383 ± 23</td>
<td>8.9 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>VR</td>
<td>10</td>
<td>122 ± 6</td>
<td>393 ± 13</td>
<td>8.6 ± 0.5</td>
</tr>
<tr>
<td>Cold stress</td>
<td>MR</td>
<td>10</td>
<td>125 ± 4</td>
<td>418 ± 12</td>
<td>9.5 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>VR</td>
<td>9</td>
<td>123 ± 4</td>
<td>411 ± 10</td>
<td>9.9 ± 0.4</td>
</tr>
<tr>
<td>Cocaine (5 mg/kg iv)</td>
<td>MR</td>
<td>3</td>
<td>111 ± 13</td>
<td>360 ± 52</td>
<td>9.6 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>VR</td>
<td>12</td>
<td>121 ± 3</td>
<td>410 ± 6</td>
<td>9.7 ± 0.4</td>
</tr>
</tbody>
</table>

Values are means ± SE. VR and MR, vascular and mixed, respectively, responders.

Fig. 1. Hemodynamic responses to 1-min exposure to cold water (4°C) in vascular (solid lines) and mixed responders (dashed lines) to cold stress. The mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), and systemic vascular resistance (SVR) responses are depicted. The initial response (occurring within the first 5 s) was used to characterize animals as vascular or mixed responders such that an increase in CO indicated a mixed responder and a decrease represented a vascular responder. Several trials were conducted on each rat to obtain an average response that was then combined with the others to obtain these results. Significant differences (*) in the initial response between vascular and mixed responders as determined by a 2-way ANOVA with a post hoc Bonferroni’s test indicating differences between individual points. b/min, beats/min.
such, differences between vascular and mixed responders at the time of the initial peak pressor response were consistent (Fig. 2). Each rat was subjected to three to ten trials (mean = 4 ± 0.3 trials).

Responses to air jet stress. Eighteen rats were also tested with air jet stress (6 trials). The startle was characterized by a pressor response resulting from highly variable cardiac output and systemic vascular resistance responses between rats. Rats were separated into vascular and mixed responders to air jet if they had mean cardiac output responses less than or greater than 1%, respectively, as previously described (23, 36). The changes in heart rate and cardiac output were significantly different (Fig. 3). The cardiac output response to cold stress was directly compared with the cardiac output response to air jet. There was a highly significant correlation ($R = 0.953, P < 0.0001$) between initial cardiac output responses to these two stressors (Fig. 4).

Responses to conditioned stress. Rats ($n = 16$) were exposed to a 15-s tone preceding a brief foot shock. After three exposures (for conditioning), hemodynamic responses to the subsequent nine trials at 10-min intervals were recorded. The onset of the 15-s tone elicited a consistent pressor response within the first 5 s in all rats that was a result of variable cardiac output and systemic vascular resistance responses as noted with air jet and cold stress. Because vascular responders to conditioned stress often had a small increase in cardiac output, animals with >2% increase in cardiac output were designated mixed responders. As noted with air jet stress, vascular responders to conditioned stress had a smaller increase in heart rate and cardiac output in response to the tone (Fig. 3). There was a significant correlation ($R = 0.656, P < 0.006$) between responses to cold stress and responses to tone preceding foot shock (Fig. 4).

Responses to cocaine. Cocaine administration (5 mg/kg iv over 45 s) elicited pressor responses in 15 rats that were mediated either by a substantial increase in systemic vascular resistance (vascular responders) or by a smaller increase in vascular resistance and no change or an increase in cardiac output (mixed responders). Rats were considered vascular responders if...
their cardiac output response was less than $-8\%$ and mixed responders if they had smaller decreases or increases in cardiac output as previously described (4).

The hemodynamic responses at the time of the maximum change in cardiac output were characterized by a pattern similar to that evoked by the three stress paradigms (Fig. 3), although there were fewer vascular responders compared with mixed responders using cocaine as a stimulus due to differences in distribution and the arbitrary cutoff value separating vascular and mixed responders.

We compared directly the initial cardiac output responses to cold stress with the maximal cardiac output responses to cocaine. There was a significant correlation ($R = 0.636, P < 0.01$) in the pattern of cardiac output responses in individual rats (Fig. 4).

### Hemodynamic Responses to Cold Stress after Selective Receptor Antagonists

We examined the effects of specific receptor antagonists on hemodynamic response patterns to cold stress. We chose to examine the effects of several drugs that alter the hemodynamic response profile to cocaine, including propranolol, nicardipine, and atropine.

Administration of propranolol (1 mg/kg iv) elicited a small increase in arterial pressure and a reduction in heart rate and cardiac output (Table 2). The increase in arterial pressure resulted from an increase in systemic vascular resistance. Subsequent exposure to cold water resulted in similar initial pressor responses and bradycardia (Fig. 5). The initial decrease in cardiac output in vascular responders was unchanged, but mixed responders were no longer different from vascular responders because they also had a decrease in cardiac output. This coincided with a greater increase in systemic vascular resistance in mixed responders (Fig. 6). The delayed hemodynamic responses were altered by propranolol such that the pressor response was enhanced and the tachycardia was abolished.

Administration of nicardipine (25 μg/kg iv) reduced arterial pressure and heart rate in six mixed and nine vascular responders (Table 2). The responses to cocaine alone revealed a significantly greater pressor response in vascular responders and a tachycardia (Fig. 5). The initial decrease in cardiac output in vascular responders was unchanged, but mixed responders were no longer different from vascular responders because they also had a decrease in cardiac output. This coincided with a greater increase in systemic vascular resistance in mixed responders (Fig. 6). The delayed hemodynamic responses were altered by nicardipine such that the pressor response was enhanced and the tachycardia was abolished.

Administration of atropine methylbromide (0.5 mg/kg iv) produced a significant increase in heart rate without affecting other measured parameters in six mixed responders.

### Table 2. Change in baseline values after pretreatments

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>n</th>
<th>Arterial Pressure, mmHg</th>
<th>Heart Rate, beats/min</th>
<th>Cardiac Output, % change</th>
<th>Systemic Vascular Resistance, % change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol (1 mg/kg)</td>
<td>MR</td>
<td>5</td>
<td>$10 \pm 3$</td>
<td>$-88 \pm 18$</td>
<td>$-6.8 \pm 3.1$</td>
<td>$15.9 \pm 2.2$</td>
</tr>
<tr>
<td></td>
<td>VR</td>
<td>6</td>
<td>$6 \pm 2$</td>
<td>$-72 \pm 13$</td>
<td>$-11.1 \pm 4.3$</td>
<td>$19.1 \pm 6.8$</td>
</tr>
<tr>
<td>Nicardipine (25 μg/kg)</td>
<td>MR</td>
<td>6</td>
<td>$-2 \pm 2$</td>
<td>$-8 \pm 11$</td>
<td>$-4.0 \pm 1.4$</td>
<td>$2.0 \pm 2.1$</td>
</tr>
<tr>
<td></td>
<td>VR</td>
<td>9</td>
<td>$-6 \pm 1$</td>
<td>$-27 \pm 6$</td>
<td>$-2.4 \pm 4.3$</td>
<td>$-10 \pm 5.0$</td>
</tr>
<tr>
<td>Atropine (0.5 mg/kg)</td>
<td>MR</td>
<td>6</td>
<td>$2 \pm 3$</td>
<td>$47 \pm 8$</td>
<td>$2.6 \pm 1.9$</td>
<td>$0.6 \pm 4.3$</td>
</tr>
<tr>
<td></td>
<td>VR</td>
<td>6</td>
<td>$7 \pm 3$</td>
<td>$60 \pm 6$</td>
<td>$-1.1 \pm 2.2$</td>
<td>$7.3 \pm 2.2$</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SE.
responders and six vascular responders (Table 2). Subsequent cardiac output responses to cold stress were attenuated in vascular and mixed responders (Fig. 6), and the increase in heart rate was enhanced.

DISCUSSION

These results suggest that rats, similar to humans, respond to behavioral stress with similar patterns that vary between individuals. Either conditioned or unconditioned stressors were capable of evoking a pattern of hemodynamic responses that varied between animals but was consistent within animals. Furthermore, we reported that other stimuli, including intravenous administration of cocaine, desipramine, amphetamine, bromocriptine, or ethanol will evoke response patterns similar to those elicited by acute stress (4, 26, 35). The wide variety of stimuli capable of evoking disparate responses in the population suggests that the initial response to stress and to psychoactive agents has common characteristics that may be a general response to arousal because these drugs have psychoactive components (28). We propose that the response pattern is inherent and/or learned in individuals.

There is controversy as to whether there is a generalized autonomic response to behavioral stress. Cannon's early studies (7) defined many adaptive responses to stress, noting a response pattern characterized by a pressor response, visceral vasoconstriction, skeletal muscle vasodilation, mydriasis, and an alerting response. He noted a close relationship between behavioral and physiological responses that he named the “General Adaptive Syndrome.” Similar hemodynamic response patterns have been noted in animals using a variety of stressors (1, 20, 42).

More recently, investigators have argued that various stressors elicit distinct patterns of autonomic responses (16, 29). For example, it is well known that the pattern of plasma catecholamine responses to different stressors varies greatly (16). While it is clear that different stressors and psychoactive agents evoke...
unique patterns of sympathetic and adrenal responses, our data suggest that some of the initial autonomic responses to acute stress may be similar. The similarity in the initial responses (during the first 5–10 s) suggests that they may be mediated by acute responses of the sympathetic nervous system. Humans also have different patterns of cardiac output and systemic vascular resistance changes to a variety of acute stressors including mental arithmetic stress and the cold pressor test (6, 10, 17). These data support the hypothesis that at least some of the initial autonomic responses to behavioral stress are similar in humans and rats.

In contrast, the prolonged hemodynamic responses to stress or cocaine varied greatly. This was likely due to the duration of the stressor itself and the nature of the stress. For example, we reported that cocaine produced a modest increase in arterial pressure associated with a bradycardia after the initial large pressor response (4, 21). In contrast, cold stress produced a sustained increase in arterial pressure with a robust tachycardia. Therefore, the delayed responses to psychostimulants or to acute stress exposure are likely to be quite different, as suggested by the varying sympathetic and plasma catecholamine responses to different stressors (16).

There is an alternative explanation for the similarity in the acute response patterns to acute stress or administration of psychoactive agents. The stressors used each had a “startle” component because they were administered without warning to the rat. Even the model of conditioned stress required presentation of a loud tone without warning. Likewise, the administration of intravenous drugs was done slowly and without warning. As such, it is possible that the rat only perceived the stimulus when the drug entered the brain to elicit its psychoactive effects. In other words, the drugs may have also elicited a response similar to a startle response. While this may limit the ability to generalize these responses as reflecting a hemodynamic pattern to stress, it does not detract from the findings that both acute stressors and drugs may evoke similar patterns of responses under these conditions.

We obtained further evidence that the responses to acute cold stress were related to those evoked by cocaine using selective receptor antagonists. Our data demonstrate that pretreatment with propranolol resulted in an enhanced reduction in the cardiac output response to cold stress, particularly in mixed responders. We reported that propranolol pretreatment enhances the decrease in cardiac output and increase in systemic vascular resistance in vascular responders to cocaine and promotes a decrease in cardiac output in mixed responders that is associated with a greater increase in systemic vascular resistance (4, 25). Others have shown that propranolol enhances coronary vasoconstriction and toxicity to cocaine administration (30, 43). Therefore, β-adrenergic receptor blockade appears to exacerbate the presumably detrimental response of enhanced increases in vascular resistance and decreases in cardiac output. The greater increase in systemic vascular resistance may be a result of the blockade of β-adrenergic receptor-mediated skeletal muscle vasodilation (25). This may also be a result of a central nervous system action because intracerebroventricular administration of propranolol causes similar changes in the hemodynamic response profile to cocaine (12). In any case, it appears as though propranolol pretreatment alters hemodynamic response patterns to cold stress in the same manner as responses to cocaine.

We also demonstrated that several agents attenuate the decrease in cardiac output elicited by cocaine in vascular responders. In this study, we report that the calcium channel blocker nicardipine (25 μg/kg iv) reduced the decrease in cardiac output and prevented the differences between vascular and mixed responders in both cardiac output and systemic vascular resistance responses to cold stress. In a similar manner, nicardipine (25 μg/kg), nifedipine (100 μg/kg), or verapamil (150 μg/kg) prevented the decrease in cardiac output and attenuated the increase in systemic vascular resistance responses to cocaine in vascular responders (21, 25). These data demonstrate that the hemodynamic responses are dependent on calcium channel activation that promotes vascular smooth muscle contraction. They also substantiate the similarity in response patterns between cold stress and cocaine.

Administration of atropine methylbromide, a peripherally acting anti-muscarinic agent, also reduced the decrease in cardiac output and the increase in systemic vascular resistance noted in vascular responders to cold stress such that there was no longer any differences in responses in mixed responders. We previously reported that atropine prevents the differences in responsiveness between vascular and mixed responders to cocaine (26). We proposed that the blunted increase in vascular resistance to cocaine after atropine pretreatment may result from blockade of muscarinic inhibition of catecholamine release (31). This could reduce the α1-mediated vasoconstrictor effects ameliorating the increase in systemic vascular resistance. We report that atropine prevented the larger increase in systemic vascular resistance to cold stress similar to responses noted with cocaine.

The present results suggest that the initial hemodynamic responses to cold stress evoke variable hemodynamic responses in a population that are correlated with responses to other acute stressors and to cocaine administration. The advantages of cold stress as a stimulus are that it is relatively easy to administer, the responses elicited are robust and comparable in magnitude to those elicited by cocaine, the responses are reproducible with repeated exposure, and the test does not require administration of a pharmacological agent that may have long-term effects on receptors due to its prolonged presence in the animal.

Although the underlying causes of variable hemodynamic response patterns remain to be determined, our data suggest that the differences between mixed and vascular responders are dependent on differences in sympathetic responsiveness. We noted that cocaine elicited a brief initial increase in sympathetic nerve activity in vascular responders that was substantially
greater than that observed in mixed responders (5). While these studies were performed in chloralose-anesthetized rats, the data still support the contention that sympathetic hyperresponsiveness may be the cause of differences. This would explain why vascular responders would be more prone to the development of hypertension and more likely to develop cardiomyopathies. Exaggerated sympathetic responses to a cold pressor test have also been noted in borderline hypertensive patients (34). It remains to be proven that greater sympathetic reactivity and its effect on arterial blood pressure and the myocardium are responsible for the differences noted in humans and rats.

The significance of varying autonomic response patterns has been investigated in humans. Others have suggested that differential autonomic responses to stress correlate with the incidence of stress-related sudden cardiac death (3, 13, 33, 39, 45). Selye (40) noted the potential significance of the relationship between behavioral stress and cardiomyopathies, noting that stress induces cardiomyopathies independent of coronary artery disease and that these are exacerbated by corticosteroid administration. This was considered a failure of the General Adaptation Syndrome described earlier by Cannon (7). Selye (40) reported that stress produces irreversible necrotizing lesions of the myocardium in sensitive individuals. Indeed, several studies report a greater incidence of myocardial lesions in humans subjected to unusual stress (8, 14, 18). Humans also have different patterns of cardiac output and systemic vascular resistance responses to stress (6, 10, 17) that are consistent within individuals (19). Eliot (13) proposed that humans responding to stress with an increase in vascular resistance (hot or vascular reactors) are at greater risk for cardiac disease (13). We demonstrated that vascular responders to cocaine are predisposed to more severe cardiomyopathies (23). Therefore, the acute hemodynamic response to stress may reflect the predisposition to cardiomyopathies as described in humans.

Vascular responders to acute stress have also been reported to be more susceptible to developing hypertension (16, 32, 41, 44). Studies in humans have shown that acute stress elicits a rise in arterial pressure that is enhanced in borderline hypertensive patients or in those patients with a family history of hypertension compared with controls (32, 41). Likewise, we noted a greater pressor response to cold stress in vascular responders compared with mixed responders (Fig. 3). Repeated cocaine produced sustained increases in arterial pressure in vascular responders but not mixed responders (4). We also reported that repeated stress produces an increase in arterial pressure that is sustained for at least 3 wk after stress in vascular but not mixed responders (36).

Perspectives

Our data support the proposal that this animal model of varying responsiveness reflects both functional and pathological variability in myocardial responses noted in humans. Therefore, this model may provide an important tool in identifying the causes of predisposition to heart disease and hypertension (28). Considering the widespread incidence of cardiovascular disease, the causes have been a major interest in biomedical research. We suggest that these differences may result from differences in sympathetic responsiveness between individuals such that vascular responders have greater sympathetic responsiveness. Further studies are necessary to address this hypothesis.

This report was prepared with the assistance of E. L. Winkeler. These studies were supported by National Institutes of Health Grant DA-05180.

Some data in the present manuscript were published recently in preliminary form (27).

REFERENCES


