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Review of Evidence for a Novel Model of Cocaine-Induced Cardiovascular Toxicity

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KNUEPFER, M. M. AND P. J. MUELLER. *Review of evidence for a novel model of cocaine-induced cardiovascular toxicity.* PHARMACOL BIOCHEM BEHAV **63**(3) 489–500, 1999.—Cocaine is known to produce life-threatening cardiovascular complications in some but not all individuals. This review considers the premise that an appropriate animal model for cocaine-induced cardiotoxicity should be characterized by varying sensitivity in the population to the deleterious effects of cocaine. We have studied such a model in which physiological, biochemical, and pathological sensitivity to cocaine varies in rats. Our studies have identified a subset of rats that respond to cocaine with a decrease in cardiac output and a substantial increase in systemic vascular resistance (named vascular responders). In contrast, another group, designated mixed responders, is characterized by a smaller increase in systemic vascular resistance and a small increase in cardiac output. We reported that vascular responders are more likely to develop hypertension and cardiomyopathies with repeated cocaine administration. Under chloralose anesthesia, vascular responders have more profound pressor responses to cocaine and an initial brief spike in renal sympathetic nerve activity not usually noted in mixed responders. Vascular responders have higher resting and cocaine-induced dopamine turnover in the striatum. In addition, vascular responders have higher alpha-adrenergic vasoconstrictor tone, whereas mixed responders have higher adrenergic cardiac tone. The difference in cardiac output and systemic vascular resistance responses to cocaine in these two subsets of the population can be prevented by L-type calcium channel, muscarinic, or alpha-adrenergic blockade. Similar hemodynamic response variability is noted with other psychoactive agents and with acute stress, suggesting that the response patterns are not unique to cocaine. We propose that individual hemodynamic response variability is dependent on differences in CNS responsiveness and correlated with the incidence of cardiovascular disease. © 1999 Elsevier Science Inc.

Cardiac output Systemic vascular resistance Hemodynamic response variability Cocaine-induced toxicity Drug abuse Behavioral stress Population differences

HEMODYNAMIC EFFECTS OF COCAINE VARY IN HUMANS

Cocaine is a widely used drug that produces both euphoria and several characteristic cardiovascular responses in humans. Cocaine administration produces an increase in arterial pressure and highly variable increases in heart rate in humans (26,27). The increase in arterial pressure is due to increased vascular resistance and cardiac stimulation (53,72). The hemodynamic and some subjective effects of cocaine are relatively short-lived and, as with other sympathomimetics, characterized by tachyphylaxis. During the past 2 decades, there has been an increase in cocaine use in the United States along with a corresponding increase in the incidence of cardiotoxicity (50,73,108). Additional complications associated with cocaine use include arrhythmias, apparent myocardial ischemia, hypertensive crises, and other life-threatening events (45,46, 53,72).

Perhaps the greatest challenge in understanding the causes of cocaine-induced sudden cardiac death or apparent myocardial ischemia is the apparent lack of a dose–response relationship as exemplified by a high degree of individual variability in responsiveness to cocaine. Cocaine elicits substantial electrocardiographic abnormalities (72) and widely variable (no change to >60% increase) responses in coronary vascular resistance of human subjects (28,64,65). The occurrence of cocaine-induced cardiomyopathies is not closely related to the dose, route of administration, or plasma levels of cocaine (46,72,108), or to the incidence of morbidity (73,98,110). These findings suggest that individual variability to cocaine-

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induced hemodynamic responsiveness and cardiotoxicity is substantial.

ANIMAL MODELS FOR COCAINE-INDUCED HEMODYNAMIC RESPONSES AND TOXICITY

To understand the mechanisms of cocaine-induced toxicity, it is necessary to develop animal models that reflect the specific responses known to occur in humans. Cocaine administration to animals produces much the same effects as noted in humans. These include a pressor response (86,93) mediated primarily by an increase in systemic vascular resistance (9,29). In anesthetized or sedated animals, cocaine elicits a decrease in cardiac output (4,5,68) and contractility (1,5,30,36,37,68,112). Furthermore, cocaine increases the susceptibility to and occurrence of arrhythmias in humans (16,45,46,53,72) and dogs (6–8,29,33, 38,47,94). Cocaine also evokes an increase in coronary vascular resistance in dogs (29,38,39,51,63,95) and pigs (24). Our laboratory has reported that cocaine induces skeletal muscle vasodilation that appears to contribute to the attenuation of cocaine's initial pressor effects in rats (9,55,58). In summary, these studies have contributed to our knowledge of the hemodynamic effects of cocaine, yet the mechanisms by which cocaine produces cardiovascular toxicity are not fully resolved.

Several investigators have suggested that these hemodynamic responses, particularly the pressor response and coronary vasoconstriction, are directly linked to toxicity (29,37,63–65,103,112), although this relationship has not been proven. Because a primary goal for studying cardiovascular effects of cocaine in animal models is to clarify the likely causes of cardiovascular toxicity associated with cocaine use in humans, a direct relationship between hemodynamic responses and toxicity would be helpful in understanding the causes of toxicity. We will briefly describe three common models for studying the cardiotoxic effects of cocaine and their limitations.

Toxicity Studies

In one experimental approach, toxic doses of cocaine are administered to animals (usually rats) to note the arterial pressure and heart rate responses as well as the pharmacologic interventions that might prevent death (14,21,34,40,71, 91,99,104,105,113,114). These models might be considered appropriate for the relatively small numbers of cocaine-related deaths (e.g., body packers) that occur after unusually high doses are ingested (101). This approach would not necessarily identify the more common cause of adverse responses noted in some humans at relatively low doses. These studies are also typically limited by recording only arterial pressure and time until seizures and death ensue, thus precluding definitive conclusions regarding the mechanisms of toxicity.

Anesthetized Animals

A second, more common model is the anesthetized animal, typically the pentobarbital-anesthetized dog or rat. In dogs, many cardiac variables can be directly measured in order to obtain a detailed description of the hemodynamic responses to cocaine (1,4,30,36,37,39,55,68,112). Despite these advantages, the common use of pentobarbital in this model (1,4,32,37,39,68,112) results in hemodynamic responses that are often different from those observed in conscious animals. Therefore, this model may not reflect the actual pattern of hemodynamic responses in the conscious animal or human (29,51,86,94,102,111). For example, the pressor and heart rate responses to cocaine in rats were largely blunted by pentobarbital, and in some cases reversed in direction (2,86). Chloralose anesthesia produces somewhat less reduction in hemodynamic responses, although many responses are still depressed (30,55). Fraker et al. (29) reported that decrease in regional ejection fraction and increase in coronary vascular vasoconstriction was not altered by sedation with pentobarbital, but the pressor, heart rate, and coronary flow were significantly reduced. We noted that the cocaine-induced hindquarters vasodilatation is not altered by dial-urethane (diallybarbiturate and urethane) anesthesia in rats but arterial pressure and mesenteric vasoconstriction were reduced (58). Therefore, it is as yet unclear whether interventions or mechanistic studies using anesthetized animals would be predictive of clinical results or outcomes.

Conscious Animals

A third model used is the conscious animal, usually dog or rat. These models typically reflect hemodynamic responses noted in humans, although, like toxicity studies, most studies are limited to blood pressure and heart rate determination because chronic instrumentation for detailed measurement of cardiac function is technically difficult, particularly in rats, and therefore, fewer investigators are capable of conducting these studies. Nonetheless, these studies appear to have the best possibility of mimicking the responses noted in humans and, therefore, adding to our understanding of the mechanisms by which cocaine produces hemodynamic responses and toxicity. The major drawback of these studies appears to be that the hemodynamic responses recorded are not only limited but are not clearly associated with the signs and symptoms of cardiac dysfunction noted in humans. For example, in animal models the pressor response is often suggested to reflect the relative toxicity of cocaine. However, the pressor response to cocaine is the result of both cardiac and vascular actions and, therefore, does not indicate whether hemodynamic responses associated with cardiotoxicity in humans are a result of alterations in cardiac function or actions in the vasculature. In other words, there is not a clear association between the parameters measured in animals and the apparent myocardial ischemia observed in some humans. Therefore, it is difficult to study the possible mechanisms of cocaine-induced toxicity without a demonstrated relationship between the hemodynamic responses measured and the occurrence of toxicity.

Because humans exhibit great variability in hemodynamic responses and susceptibility to cocaine-induced toxicity (28, 45,46,64,65,72,73,98,110), it is necessary to identify an animal model wherein individual animals respond somewhat differently to cocaine. As mentioned above, it would be equally as important to find differences that are related to an index of toxicity. Despite these concepts, most reports describing animal models of cocaine toxicity do not describe highly variable responses. A few exceptions exist, including descriptions of differential susceptibility to cardiomyopathies in rats (69) and to vascular lesions in rabbits (66), to the susceptibility to hyperthermia (44) and to the levels of free [Mg^{++}] in the brain (3). The individual variability in sensitivity to stress or drug administration noted in animals may be overlooked by most investigators because extreme values may result from experimental errors. Furthermore, the consideration of subsets of individual animals requires a substantially larger population greatly increasing the costs and time necessary to perform studies. Despite these caveats, a model reflecting specific variability of cardiovascular parameters would aid in examination of the cause of variable toxic responses in humans.

PROPOSED MODEL OF HEMODYNAMIC VARIABILITY TO COCAINE

Recent studies in our laboratory have revealed differences in hemodynamic, biochemical, and morphological responsiveness to cocaine (10,11,54,56,57). Initially we noted highly variable cardiac output and systemic vascular resistance responses to different doses of cocaine in individual Sprague–Dawley rats (10). With repeated administration of cocaine, hemodynamic responses in individuals were relatively consistent yet substantial differences existed between individuals. In some rats, cocaine elicited an increase or no change in ascending aortic blood flow, whereas other rats had relatively consistent decreases. To facilitate analysis of this variability, we arbitrarily divided these rats into two groups. We named the former group, with a smaller increase in vascular resistance and little change or a small increase in cardiac output, mixed responders, and the latter group, with a decrease in cardiac output and a greater increase in vascular resistance, vascular responders (in early manuscripts, these were designated nonresponders and responders, respectively). Because the pressor response to cocaine does not differ in these two groups, the calculated increase in systemic vascular resistance is significantly greater in vascular responders. The responses of these two groups to 5 mg/kg cocaine are shown in Fig. 1.

Our studies have been designed to identify the primary cause of the difference in responsiveness. Specifically, we have attempted to determine whether the difference is due to an effect on the myocardium or on the vasculature or a combination of these variables. We have noted these phenomena in a large population of rats (>200) to date. The distribution of rats administered 5 mg/kg cocaine (over 45 s) and to 0.5 mg/kg (bolus injection) are shown in Fig. 2. Because the distribution of the cardiac output responses to cocaine (5 mg/kg) appeared biphasic, we separated rats into mixed and vascular responders as shown. Subsequent studies revealed several parameters that covary with the cardiac output responsiveness. The remainder of this review will describe the specific findings we have made in trying to elucidate the causes of these apparent differences in hemodynamic responsiveness.

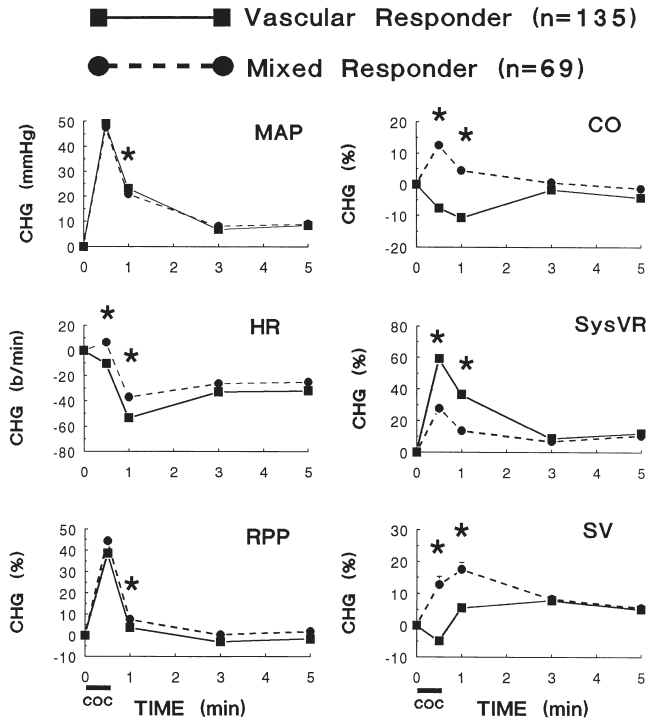

FIG. 1. Effects of cocaine (5 mg/kg, IV over 45 s, INJ) on mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), and systemic vascular resistance (SysVR) in 69 mixed responders and 135 vascular responders. The mean ± standard error is depicted at different time points, although the standard errors are often very small. Data were compared with a two-way analysis of variance. Significant differences ($p < 0.05$) between vascular and mixed responders are denoted by asterisks. The differences may appear minute due to the large amount of data utilized to generate this figure.

RELATIONSHIP OF HEMODYNAMIC VARIABILITY TO CARDIOVASCULAR DISEASE

In early studies with rats given varying doses of cocaine, we noted widely variable alterations within myocardiocytes including alterations in the sarcoplasmic reticulum and the myofibrils that appeared to correlate with the cardiac output responsiveness. It appeared that vascular responders had more significant alterations, particularly dilatation of the sarcoplasmic reticulum, compared to mixed responders and saline-treated rats (unpublished observations). Subsequently, we studied a series of rats both with and without ascending aortic flow probes and with repeated cocaine (5 mg/kg, twice daily) or saline (vehicle) for 2 weeks of treatment (56). As before, we noted substantial variability in the cardiovascular responses to cocaine and in the morphologic alterations noted in the myocardium. The most common alteration noted was a dilated sarcoplasmic reticulum (Fig. 3A), although many instances of hypercontracted myofibrils (Fig. 3B), focal lesions with edema, and mitochondrial alterations were also noted. In contrast, fewer alterations and less severe dilatations of the sarcoplasmic reticulum were noted in mixed responders (Fig. 3C). We reported a significant correlation between the extent of sarcoplasmic dilatations, determined blindly, and the car-

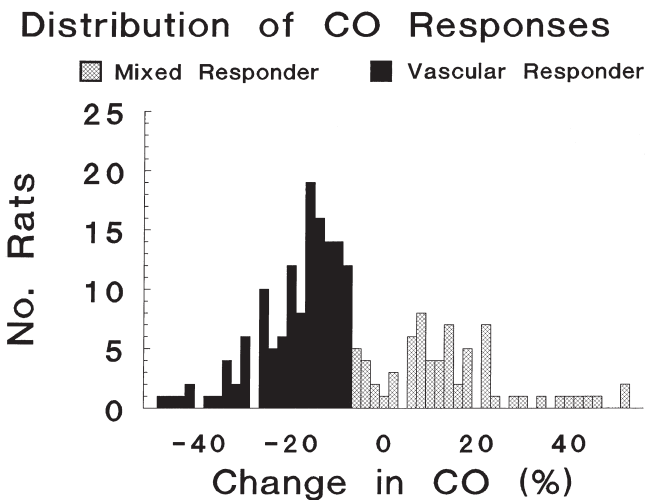

FIG. 2. Distribution of mean cardiac output responses in a population of rats. Cocaine (5 mg/kg, IV) was administered to each rat to characterize the hemodynamic responses. The maximum change in cardiac output occurring within the first 3 min after cocaine (usually within the first minute) was determined. The mean maximum change was derived for each rat after 3–14 trials. The distribution was used to arbitrarily separate rats into mixed (crosshatched bars) and vascular (filled bars) responders as shown.

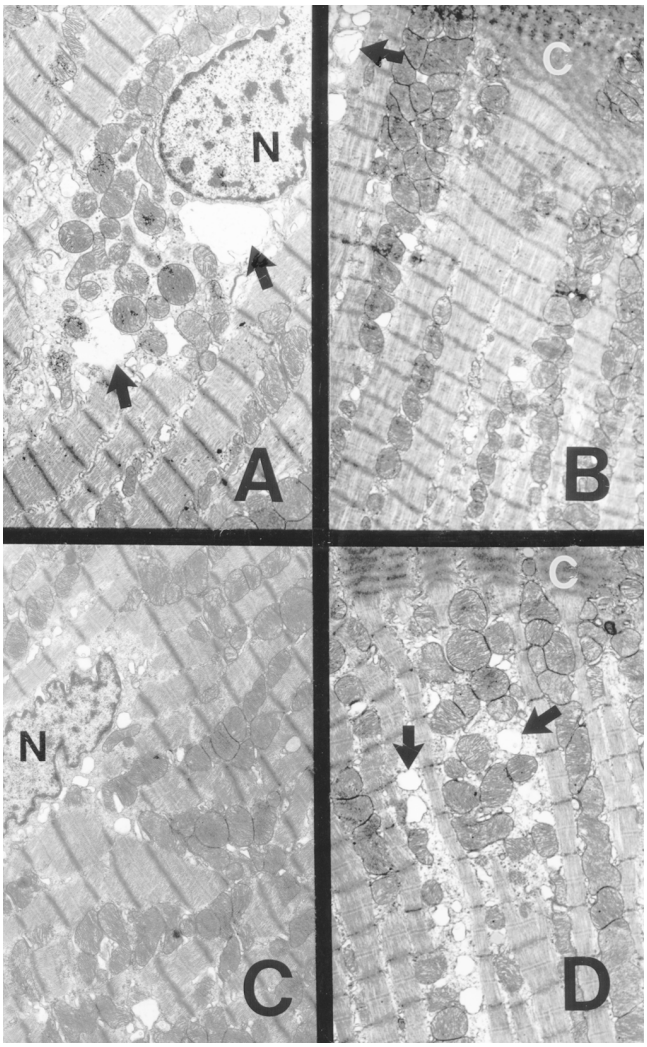

FIG. 3. Myocardial tissue from vascular responders (A,B) treated with cocaine (5 mg/kg, twice daily) for 2 weeks compared to tissue from a mixed responder treated similarly (C). The extent and severity of the sarcoplasmic reticular changes were determined blindly using a scale of 0 (no change) to 3 (severe alterations). These correlated with the decrease in cardiac output (56). Hypercontracted myofibrils and focal necrosis were also observed. In a different experiment, acute air jet stress was utilized to characterize rats as mixed or vascular responders. Myocardial tissue from a vascular responder to air jet stress is shown 18 h after a 1-h restraint stress exposure (D), demonstrating strikingly similar alterations. Identified structures include: C, hypercontracted myofibrils; N, nucleus; arrows, dilated sarcoplasmic reticulum.

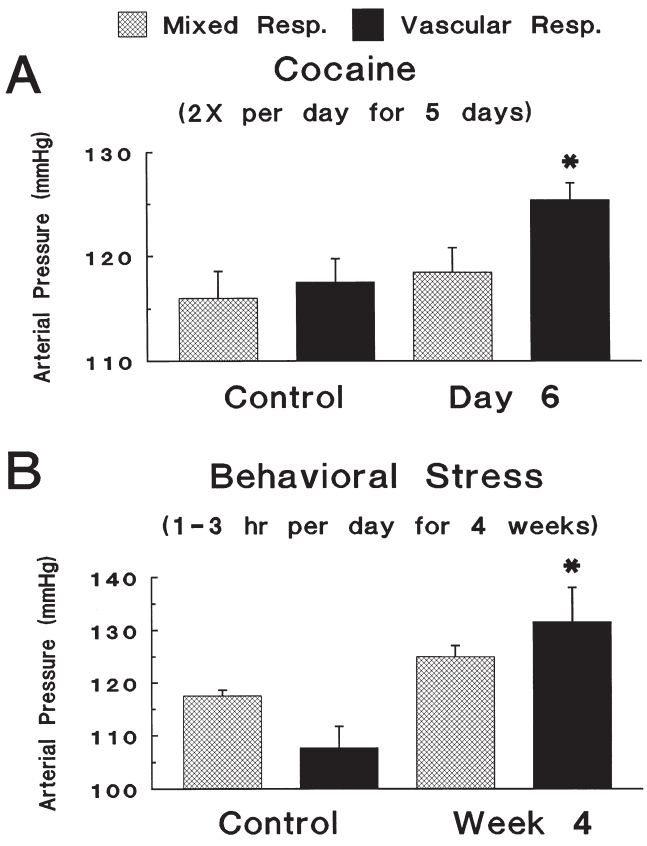

FIG. 4. The effects of repeated cocaine (A) and repeated stress (B) on resting arterial blood pressure in mixed and vascular responders (crosshatched and filled bars, respectively). Rats were treated with cocaine (5 mg/kg, IV, twice daily, 3 h apart) for 5 days while measuring hemodynamic responses. On the sixth day before cocaine administration (18–20 h after the previous cocaine administration), resting arterial pressure was elevated in vascular responders but not mixed responders (11). In a separate experiment, rats were exposed to a 15-s tone preceding a brief (<1 s) foot shock (12 trials). These data were used to classify rats as mixed or vascular responders. Subsequently, rats were exposed to repeated stress for 4 weeks. Each day rats were exposed to 1 h of cold stress (1-cm deep water at 4°C), 1 h of restraint stress (in a Plexiglas tube) or 3 h of tone preceding brief foot shock at 5-min intervals. The stressors were varied daily for 6 days a week for 4 weeks such that each rat was exposed to each stressor eight times. Two days after the last stress exposure, resting arterial pressure was elevated in vascular responders compared to mixed responders as determined by analysis of variance.

diac output responsiveness in individual rats with significantly more ultrastructural alterations in vascular responders compared to mixed responders (56). This relationship demonstrates the first evidence for a direct correlation between functional and pathological responsiveness to cocaine. Moreover, these studies illustrate the importance of analyzing response variability within a population.

In retrospective studies, we have noted that some rats receiving multiple cocaine injections may develop hypertension, at least acutely. Studies on rats treated with cocaine (5 mg/kg, IV, twice daily) for three (n = 26) or 6 days (n = 28, Fig. 4) have revealed that, on the following day (18–20 h after last treatment), arterial pressure is significantly elevated in vascular responders but not mixed responders [(11); Fig. 4A]. This occurs despite the relatively short half-life (15–20 min) of cocaine in rats (84). These findings suggest that vascular responders may also be more susceptible to cocaine-induced hypertension.

DETERMINANTS OF VARIABLE HEMODYNAMIC RESPONSES

We have identified several other functional indices of differential sensitivity to cocaine that are related to the cardiac output/systemic vascular resistance responses in individuals. These have been utilized to understand the mechanisms by which responses vary in individuals.

Sympathetic Nerve Discharge

Several investigators have reported that cocaine elicits a profound decrease in sympathetic activity in conscious and anesthetized rats (2,55), decerebrate and anesthetized cats (88), and anesthetized dogs (32). We noted a brief spike in renal sympathetic nerve activity before the prolonged sympathoinhibition in some chloralose-anesthetized rats (55). In a subsequent study, we characterized rats as vascular or mixed responders and then anesthetized them with chloralose to study their responsiveness to cocaine while measuring arterial pressure, heart rate, and renal sympathetic nerve activity (12). There was a significantly greater increase in arterial pressure and a smaller decrease in heart rate in vascular responders after cocaine administration (Fig. 5). Although all rats had a sustained decrease in sympathetic nerve activity, there was a greater likelihood of a brief (2–12 s), initial spike in renal sympathetic nerve activity in vascular responders (10 of 11 tested) compared to mixed responders (3 of 9 tested). Abrahams, Cuntapay, and Varner (2) noted a brief spike in renal sympathetic activity preceding the sympathoinhibition in response to cocaine in conscious rats. The increase in activity was of similar duration to that noted by us in chloralose-anesthetized rats (12,55). The significance of such a brief spike is difficult to determine, but our experiments suggest that it is, at least, more likely to occur in vascular responders. As yet, we do not know whether it is responsible for the cardiovascular responses or the cardiomyopathies related to cocaine administration. Randall et al. (90) demonstrated a much shorter (approximately 400 ms) burst of renal sympathetic nerve activity that preceded a prolonged pressor response to acute behavioral stress. Therefore, the sympathetic activity is likely to be responsible, at least in part, for the hemodynamic responses. Cocaine also elicits an increase in plasma catecholamine levels (17,52). In addition, several investigators have reported that ganglionic blockade dramatically reduces the hemodynamic effects of cocaine (52,55,103). These data strongly implicate sympathetic nerves in the pressor responsiveness.

Skeletal Muscle Vasodilation

Although beta-adrenoceptors mediate cocaine-induced increases contractility and end diastolic pressure (14,64,95), we suggested that they are also responsible for cocaine-induced vasodilation following a brief alpha-mediated vasoconstriction in the hindquarters vascular bed (55,58). The skeletal muscle vasodilation could be prevented by propranolol or ICI 118,551 (β_2-adrenoceptor antagonist), reduced by adrenal demedullation but was unaffected by metoprolol [(9,55); Knuepfer and Gan, unpublished results]. We concluded that the vasodilator response was mediated by beta$_2$-adrenergic mechanisms. Because ibuprofen could also antagonize these effects, eicosanoids may also contribute to these responses (58). There is also likely to be passive vasodilation mediated by reduced sympathetic tone because lumbar sympathetic nerve activity is reduced by cocaine (55).

We also noted a high amount of variability in the magnitude of the hindquarters vasodilator response compared to the mesenteric vasoconstrictor response (unpublished results). Because this response coincides with the decrease in cardiac output noted in vascular responders, we have undertaken studies to examine the relationship between the skeletal muscle vasodilation and the cardiac output/systemic vascular resistance response pattern on the premise that greater vasodilation in some animals might attenuate the increase in systemic vascular resistance and result in a mixed responder and vice versa. Although our initial results are preliminary, it appears as though the hindquarter vasodilatory effects are related to the cardiac output responses (Knuepfer and Gan, unpublished results), suggesting that differential responsiveness may be due to variability in the rat's ability to evoke skeletal muscle vasodilation.

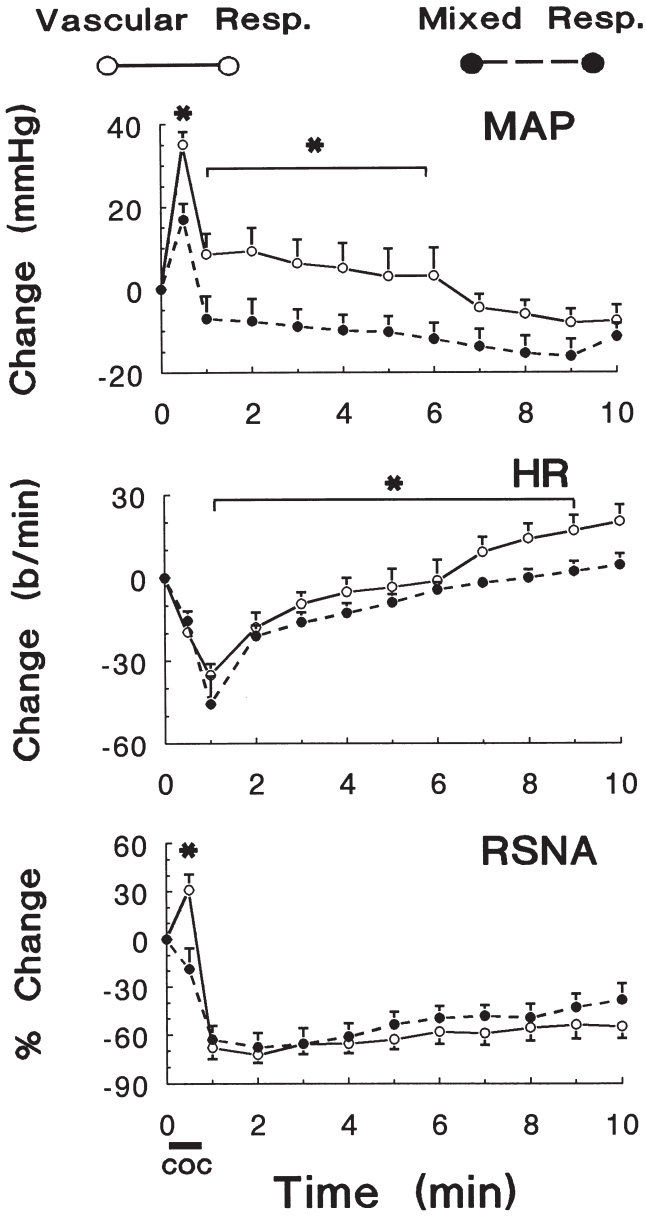

FIG. 5. Responses to cocaine administration in chloralose-anesthetized rats. Cocaine (5 mg/kg, IV) was administered to vascular and mixed responders while recording hemodynamic parameters. Abbreviations other than renal sympathetic nerve activity (RSNA) are defined in Fig. 1. Significant differences between vascular and mixed responders were determined by analysis of variance with repeated measures, and are shown as bars over the segments that differed. This figure is modified from one originally published in the Journal of Pharmacology and Experimental Therapeutics (12), and is reprinted here by permission of the publisher.

Coronary Blood Flow (Pulmonary Blood Flow)

In an effort to determine a relationship between cardiac output responses to cocaine and myocardial perfusion, we attempted to record coronary blood flow in anesthetized and conscious rats (78). We developed a technique that was capable of recording coronary blood flow velocity by carefully positioning a piezoelectric crystal in a suction probe over the coronary flow. Because the coronary artery of the rat is not visible, this required moving the probe until a phasic signal was identified. However, in subsequent studies we discovered that the velocity signal we were recording routinely was readily obtained. This was unexpected, so we performed acute experiments with this procedure with brief occlusion of the pulmonary artery (Fig. 6A) or ascending aorta. These experiments revealed that we were recording blood flow in the right ventricle and, therefore, estimating pulmonary arterial flow. Thus, in our initial report (78) and other preliminary studies using the same technique (76,77,79,80,96) we have labeled incorrectly hemodynamic response as estimates of coronary blood flow. The data from the previous work (78) actually represents an estimation of pulmonary blood flow responses to cocaine in conscious and anesthetized rats. The results of these and subsequent studies in conscious rats suggested that changes in pulmonary blood flow in response to cocaine were variable but small, and could be prevented by prazosin pretreatment and enhanced by metoprolol administration (Fig. 6B). The relationship between pulmonary blood flow responses to cocaine and susceptibility to cardiac dysfunction, however, remains to be established. We cannot conclude that cocaine causes coronary vasoconstriction in the rat, although this has been noted in dogs (29,38,39,51,63,95), pigs (24) and humans (28,64,65).

PHARMACOLOGIC STUDIES OF THE MECHANISMS OF VARIABLE RESPONSIVENESS

We have examined several possible causes of the differences between vascular and mixed responders using pharmacologic tools. We noted that prazosin treatment alone reduced arterial pressure in rats by different mechanisms (11). In mixed responders, prazosin reduced cardiac output, whereas in vascular responders, prazosin reduced systemic vascular resistance (Table 1). Likewise, metoprolol alone elicited a significant decrease in cardiac output only in mixed responders [(61); Table 1]. ICI 118,551, a $beta_2$-adrenoceptor antagonist, did not alter resting arterial pressure, cardiac output, or systemic vascular resistance in four vascular responders (Knuepfer and Gan, unpublished data). Therefore, these data suggest that resting $alpha_1$-adrenergic and possibly, $beta_1$-adrenergic cardiac and vascular "tone" is different in vascular and mixed responders.

The effect of pretreatment with specific agents on cocaine-induced responses was noted in several studies (Fig. 7). The initial brief peak pressor response was attenuated by pretreatment with several agents including pentolinium, prazosin, propranolol, ethanol, desipramine, and bromocriptine (11,59, 81). Ganglionic blockade or $alpha_1$-adrenergic receptor blockade prevents the decrease in cardiac output and the other hemodynamic responses (11,55). The calcium channel antagonists nifedipine, verapamil and nicardipine, selectively attenuate the decrease in cardiac output noted in vascular responders (54,61). The muscarinic antagonist, atropine methylbromide, also selectively reduces the decrease in cardiac output in vascular responders (60). Finally, some purported treatments for cocaine addiction, including desipramine and bromocriptine, reduced the cocaine-induced decrease in cardiac output observed in vascular responders (59). Therefore, we suggest that muscarinic (perhaps due to inhibition of cholinergic modulation of catecholamine release) and $alpha_1$-adrenergic receptors and calcium play a permissive role in the cardiac depressant effects of cocaine.

In contrast, the beta-adrenergic receptor antagonists propranolol (Fig. 7) and metoprolol reduce the pressor response to cocaine but enhance the decrease in cardiac output (54,61).

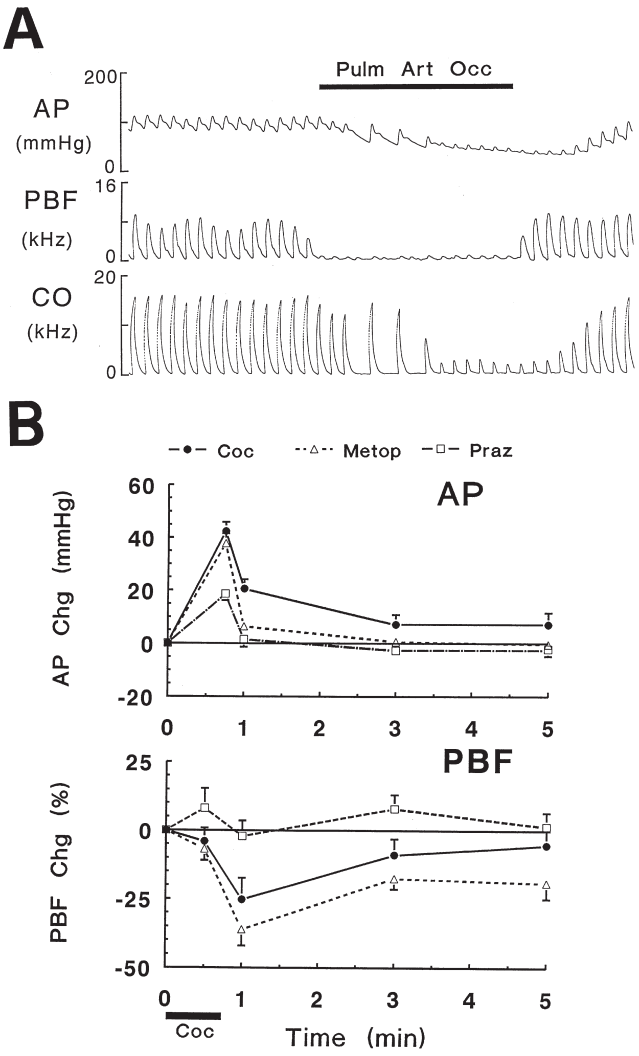

FIG. 6. In A, the effects of selective occlusion of the pulmonary artery (Pulm Art Occ) for 2 s (denoted by bar) on arterial pressure (AP), pulmonary blood flow (PBF) measured from the right ventricle and cardiac output (CO) measured from the ascending aortic flow probe in pentobarbital-anesthetized rats is shown. Transient occlusion of the pulmonary artery reduced PBF to 0 with smaller effects on cardiac output. Similar results were obtained in six other rats, demonstrating that our previous studies describing coronary flow were, in fact, a measurement of right ventricular or pulmonary flow. B shows the effects of prazosin (0.1 mg/kg) and metoprolol (1 mg/kg) pretreatment on arterial pressure and pulmonary blood flow responses to cocaine (5 mg/kg) in conscious, freely moving rats. Significant differences after pretreatment were determined by analysis of variance with repeated measures (time points). Prazosin reduced the pressor response to cocaine and the decrease in PBF. In contrast, metoprolol enhanced the decrease in PBF without affecting arterial pressure responses.

TABLE 1

CHANGES ELICITED BY PRETREATMENTS IN VASCULAR AND MIXED RESPONDERS

Drug	Dose (mg/kg)	Arterial Pressure (mmHg)		Heart Rate (b/min)		Cardiac Output (% Chg)		Systemic Vascular Resistance (% Chg)	
		VR	MR	VR	MR	VR	MR	VR	MR
Pentolinium	7.5	−30 ± 3*	−38 ± 4*	−29 ± 9*	−28 ± 9*	2 ± 4	−6 ± 4	−25 ± 2*	−29 ± 2*
Prazosin	0.1	−17 ± 2*	−23 ± 3*	32 ± 11*	30 ± 9*	−1 ± 3	−19 ± 6*	−13 ± 2*	5 ± 8
Propranolol	1.0	6 ± 4	3 ± 2	−57 ± 7*	−76 ± 12*	−4 ± 4	0 ± 6	10 ± 5	4 ± 5
Metoprolol	1.0	4 ± 5	−1 ± 1	−66 ± 9*	−66 ± 8*	−6 ± 3	−9 ± 3*	11 ± 7	9 ± 2
Atropine	0.5–1	−1 ± 2	0 ± 2	78 ± 11*	58 ± 12*	4 ± 2	2 ± 2	1 ± 4	−1 ± 2
Nicardipine	0.025	−6 ± 1*	−5 ± 1	26 ± 4*	12 ± 2	1 ± 1	−10 ± 3	−6 ± 1	10 ± 4
Bromocriptine	0.1	17 ± 4*	24 ± 6*	−7 ± 11	16 ± 13	3 ± 3	12 ± 5*	12 ± 4*	11 ± 5
Desipramine	1.0	19 ± 4*	22 ± 3*	−30 ± 7*	−6 ± 8	0.5 ± 1	13 ± 3*	16 ± 3*	7 ± 4
Ethanol	475	10 ± 3*	7 ± 3	−38 ± 9*	−3 ± 8	−3 ± 3	1 ± 1	13 ± 5*	5 ± 3
	950	14 ± 6*	14 ± 3	−43 ± 9*	−31 ± 10*	−6 ± 3*	−1 ± 3	18 ± 6*	14 ± 5*

*Significantly different ($p < 0.05$) from baseline value.

Therefore, without measurement of ascending aortic blood flow, propranolol was suggested to have beneficial effects because it ameliorated the pressor responses, and presumably the cardiovascular toxicity, associated with cocaine use (14,34, 51,100). In contrast, there is evidence that propranolol enhances cocaine-induced coronary vasoconstriction in humans (65), pigs (107), and dogs (51,95). Furthermore, it has been reported that propranolol may exacerbate cocaine-induced cardiotoxicity in humans (89,109). Therefore, there are differing views as to the critical parameters that may reflect relative susceptibility to cardiotoxicity. Our data, described earlier, documented that vascular responders are predisposed to cocaine-induced cardiomyopathies and hypertension (11,56). From these data, it appears that beta-adrenoceptors may be important in protecting the heart from cocaine-induced cardiodepression.

Several experiments have resulted in negative findings, allowing us to further understand the neurotransmitters and mechanisms that are not involved in differential responsiveness. For example, we tested several agents that are incapable of reducing the decrease in cardiac output in vascular responders. These include indomethacin, heparin, diazepam, and buprenorphine pretreatment (11,59). Furthermore, we have not observed differences in responsivity to cocaine or to catecholamines in isolated perfused hearts from vascular and mixed responders (12). There were no differences in the rate of metabolism or the relative amounts of specific cocaine metabolites in plasma or CSF samples taken 10 min after cocaine administration in conscious rats (12). Considering these data, it does not seem likely that differences in coagulatory systems, inherent adrenergic or cocaine receptors in the heart, metabolic pathways, or GABAergic sensitivity are responsible for the differential sensitivity between these animals.

SPECIFICITY OF RESPONSE PATTERNS TO COCAINE

Effects of Psychoactive Agents

We have evidence that cocaine is not the only psychoactive agent that evokes variable hemodynamic responsiveness. We reported that amphetamine elicits variable cardiac output responsiveness related directly to cocaine-induced responses in individual rats (11). More recently, we observed a variable cardiac output responsiveness to ethanol administration that is related to cocaine-induced responses [(81); Table 1]. We also noted variable responses to bromocriptine and to desipramine that covary with the hemodynamic response profile to cocaine [(59); Table 1]. The similarity of response profiles to a variety of psychoactive drugs suggests that the response profile to cocaine is not uniquely due to the particular actions of cocaine. For this reason, we examined the effects of general arousal or stress on hemodynamic response profiles.

Effects of Behavioral Stress

We reported that cardiac output responses to acute air jet stress vary in conscious rats (57). A brief air jet stress (1–2 s) elicits a pressor response in all animals that is relatively consistent, yet the cardiac output and the heart rate responses vary greatly between individuals. Although the hemodynamic responses to acute stress were short-lasting compared to responses to cocaine, rats appeared to fall into one of two groups: one with consistent increases in cardiac output (mixed responders) and the other with decreases or no change (vascular responders). The heart rate response was directly correlated with the cardiac output response with mixed responders having increases in heart rate, whereas vascular responders had a decrease or no change. After examining the maximum changes in cardiac output evoked by repeated air-jet administration in individual rats, we were able to note a bimodal distribution as with cocaine (Fig. 8A). Cardiac output responses to air-jet stress were somewhat smaller than those observed with cocaine, but they were directly correlated with cocaine-induced responses (57). Therefore, vascular responders to air-jet stress are likely to be vascular responders to cocaine, and vice versa.

More recently, we examined the effects of a conditioned stimulus (tone followed by foot shock) in conscious rats as described by Randall et al. (90). Rats had consistent changes in arterial pressure but cardiac output responses to the tone preceding the conditioned stimulus were highly variable [(35,82); Fig. 8B]. The cardiac output responses were correlated with the response profile to the unconditioned stressor, air jet. These data suggest that the hemodynamic response pattern may be a characteristic response to behavioral stress. More importantly, rats classified as vascular responders developed a sustained hypertension with repeated stress, whereas mixed responders did not [(35,82); Fig. 4B]. As discussed earlier, we

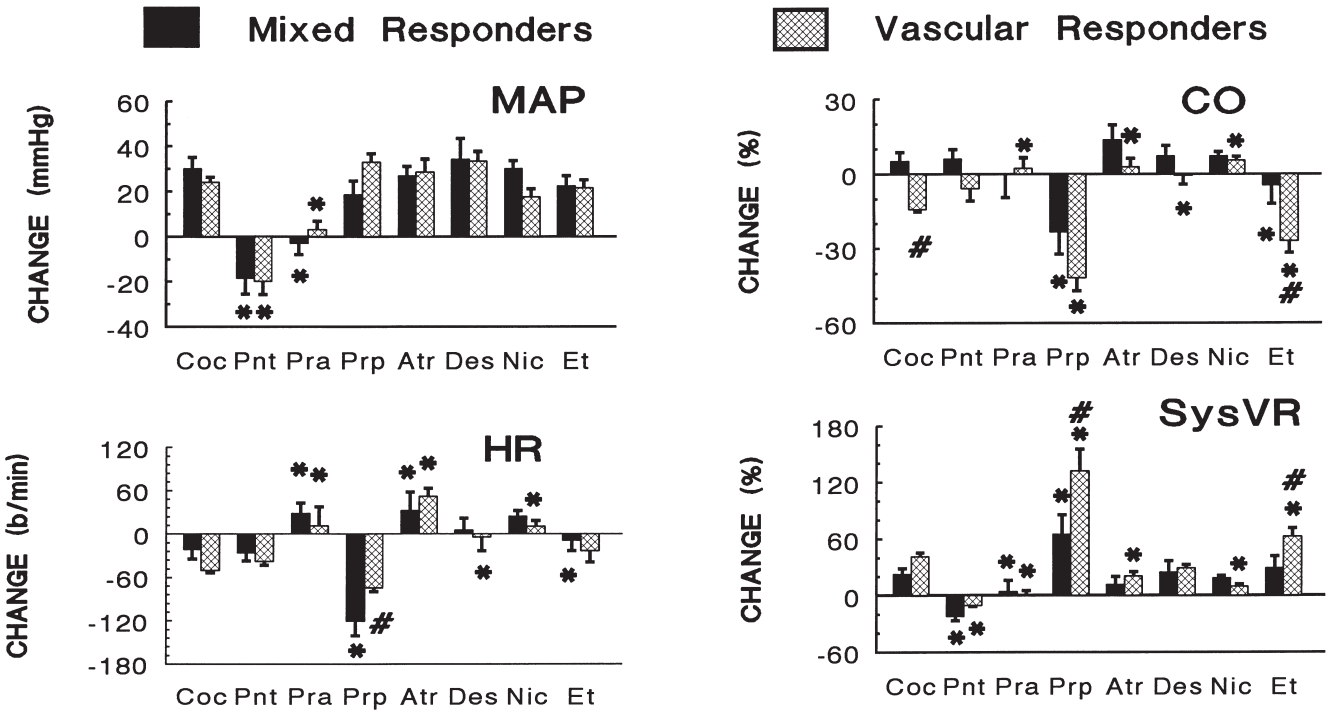

FIG. 7. Effects of several antagonists on cocaine-induced hemodynamic responses. Cocaine (Coc, 5 mg/kg, IV) was administered alone and 10 min after pretreatment with one of several agents including pentolinium (Pnt, 7.5 mg/kg, IV), prazosin (Pra, 0.1 mg/kg), propranolol (Prp, 1 mg/kg, IV), atropine methylbromide (Atr, 0.5–1 mg/kg, IV), desipramine (Des, 1 mg/kg), nicardipine (Nic, 0.025 mg/kg, IV), and ethanol (Et, 950 mg/kg). Significant differences for each group and each parameter were determined by comparing values before pretreatment to those after cocaine administration. A representative control group is shown although the analysis of variance was performed using separate control groups for each drug treatment. An asterisk denotes a significant difference from control (cocaine alone) whereas a # denotes a significant difference between vascular and mixed responders for each response.

noted that vascular responders to cocaine were also predisposed to develop hypertension [(11); Fig. 4A]. These results suggest the hemodynamic response pattern correlates with susceptibility to hypertension.

STRESS-INDUCED RESPONSE VARIABILITY IN HUMANS

The widely varying distribution of cardiac output responses to stress noted in our studies (Fig. 8) is strikingly reminiscent of results from studies in humans in response to behavioral stress. Brod (13) summarized early studies by reporting that the primary response of 22–23% of the population to mental arithmetic stress was a fall in cardiac output and an increase in peripheral vascular resistance, whereas most subjects responded to stress with an increase in cardiac output and a decrease in systemic vascular resistance. Despite these differences in hemodynamic response profiles, the pressor responses were equivalent in these two groups. Our data correspond well to evidence that humans who are classified as vascular responders to acute stress are more likely to develop hypertension (41,67,106). Recent studies also suggested that vascular responders are predisposed to cardiac disease (25). Highly variable susceptibility to cardiomyopathies after repeated or extreme stress has been reported in animals (19,20,87) and in humans (15). Likewise, we have noted variability in the morphologic responses of individual rats subjected to restraint stress (unpublished results). The alterations include signs of dilated sarcoplasmic reticulum and hypercontracted myofibrils (Fig. 3D) that are qualitatively similar to those noted after cocaine administration (56). Therefore, human cardiovascular responsiveness and predisposition to cardiovascular disease resembles similar responses in rats. For this reason, we propose that the rat may provide a model for studying the causes of variable responsiveness in humans and its relation to cardiovascular disease.

ROLE OF THE CENTRAL NERVOUS SYSTEM

We suggest that the hemodynamic responsiveness of individual rats to administration of psychostimulants is dependent in part on the behavioral perception of drug administration. This would explain why most hemodynamic responses to cocaine are dramatically altered by anesthesia (29,55,58,86, 94,111). Likewise, bromocriptine or desipramine differential cardiac output responsiveness correlates with cocaine-induced responsivity (59). Therefore, several, but not all (e.g., buprenorphine, diazepam) agents produce a similar pattern of responses that is consistent in individual rats.

Mesolimbic Dopamine Turnover

The variable responsiveness may correlate with dopamine release in the basal ganglia. Dopamine overflow is enhanced in the striatum and/or nucleus accumbens in response to cocaine (18,42,49,74), amphetamine (74,85), ethanol (43), and to acute behavioral stress (23,48). We measured dopamine, homovanillic acid (HVA), DOPAC, and other dopamine metabolites using microdialysis in the nucleus accumbens and the striatum of conscious rats in response to cocaine and to

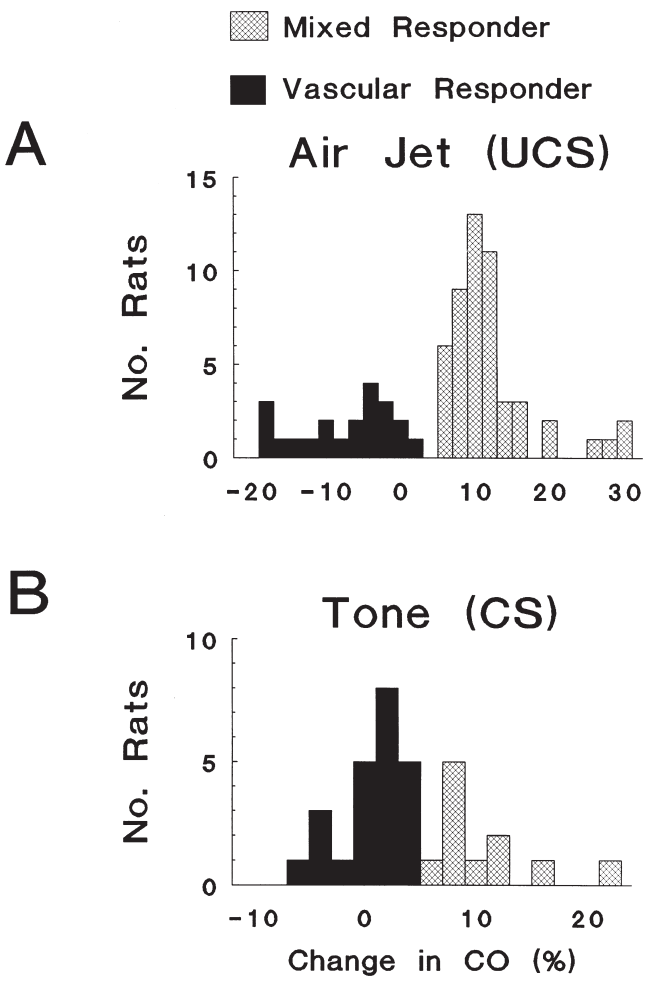

FIG. 8. Distribution of cardiac output responses to air jet (unconditioned stimulus or UCS, A) and to tone followed by a foot shock (conditioned stimulus or CS, B). Air jet was delivered to the face (20 lb/in^2, 1 cm away) of the rat six times (at 10–15-min intervals) while recording hemodynamic parameters. The maximum changes in cardiac output were determined for each rat and are presented as mean values. The data were arbitrarily divided into mixed and vascular responders (crosshatched and filled bars, respectively) according to the cardiac output response (57). In B, mean cardiac output responses were obtained by recording responses to a tone (15-s duration) presented immediately preceding a brief foot shock (<1 s) that elicited a flinch but not vocalization or sustained behavioral responses. These were divided as described for air jet and for cocaine administration into vascular and mixed responders (35,82).

acute restraint stress (62). We noted that two indices of dopamine turnover, HVA/DA and DOPAC/DA ratios, were significantly higher in vascular responders (unpublished data). Striatal dopamine overflow was enhanced by cocaine administration while DOPAC, HVA, and 5-HIAA (metabolites) were reduced. Vascular responders had greater increases in dopamine overflow and decreases in DOPAC/DA and HVA/DA ratios compared to mixed responders. Therefore, variations in dopamine turnover may reflect differences in autonomic response patterns.

Although it does not seem likely, it is possible that central autonomic responses to psychostimulants or behavioral stress could evoke opposite changes in vascular resistance and cardiac output. Using electrical and chemical stimulation of the hypothalamus, we noted a number of sites that evoke arterial pressure responses with changes in cardiac output in the opposite direction (97). This suggests that it is not uncommon for central autonomic control pathways to evoke opposing changes in cardiac and vascular function.

Finally, it is possible that variable responsiveness is a result of differing sensitivity of peripheral adrenergic pathways and/or receptor activation in different individuals. We have noted some differences in responsiveness to phenylephrine and to nitroprusside in vascular and mixed responders (12). These appear to be relatively minor compared to the magnitude of the differences in hemodynamic responses to cocaine and to stress, but may still contribute to variable responsiveness.

Role of Central CRH

Recent studies suggest that corticotropin releasing hormone (CRH) may also participate in central neuronal responses to cocaine and to stress (22). Intracerebroventricular administration of the CRH antagonists, alpha-helical CRF_{9-41} (10 μg) or astressin (5 μg), prevented the decrease in cardiac output noted in vascular responders after intravenous cocaine [(22); unpublished observations). Likewise, alpha-helical CRF_{9-41} (10 μg, ICV) administration prevented the decrease in cardiac output in response to air jet (Dong, Gan, and Knuepfer, unpublished observation). These data suggest that CRH plays a critical role in mediating autonomic response patterns to cocaine or behavioral stress.

GENETIC DETERMINANTS OF INDIVIDUAL RESPONSE VARIABILITY

There is some evidence that variable responsiveness is genetically determined (75). Investigators have noted variability in cocaine-induced cardiovascular and locomotor responses (92), hyperthermic responses (44), cardiomyopathies (69), and vascular lesions (66), suggesting genetic variability. Likewise, differences in hemodynamic and adrenal responsiveness to stress and to administration of pressor agents have been noted (13,25,41,67,70,106,115). To investigate a possible genetic component of hemodynamic responsiveness in our model, we bred vascular and mixed responders from two pairs of outbred Sprague–Dawley rats. After three generations, we were able to breed close to 100% of vascular responder offspring from vascular responder parents. Mixed responders bred together produced both vascular and mixed responders (unpublished data). Therefore, the cocaine-induced cardiovascular response variability may be genetic as with other responses and, if so, is multifactorial.

HYPOTHESIS AND SUMMARY

We reiterate the proposal stated by others that individuals vary in their predisposition to stress-induced cardiovascular disease (31,83). We hypothesize that the hemodynamic response pattern correlates with the susceptibility of individuals to cardiovascular disease, and that cocaine and some other psychoactive agents evoke similar hemodynamic response patterns. The variable autonomic responses are a result of differences in 1) central neuronal processing of the autonomic responses to the perturbation; and/or 2) peripheral autonomic receptor sensitivity. Although it is not yet clear which explanation is valid, one or more of these possibilities would explain the differences in responsivity noted to these varied drug treatments and to behavioral stress. Our data suggest

that several receptor mechanisms may be involved in central or peripheral mediation of the decrease in cardiac output noted in some animals. The muscarinic and alpha$_1$-adrenergic receptors and L-type calcium channels appear to be necessary, whereas beta$_1$- or beta$_2$-adrenergic receptors attenuate the cocaine-induced cardiodepression. Central CRH release may vary in these animals, possibly leading to variable hemodynamic responsiveness.

In conclusion, it is clear that humans express substantial variability in individual responsiveness to drugs and to behavioral stress. The present review describes an animal model of variability with specific indices of cardiovascular function (cardiac output, systemic vascular resistance, stroke volume, heart rate, plasma epinephrine levels, sympathetic nerve responsiveness) that may help predict individual rats at higher risk for cardiotoxicity and hypertension. The differential sensitivity is likely to be genetically determined. It is not known whether there is a relationship between cardiovascular responsiveness and cardiotoxicity in humans, but there are striking similarities in individual hemodynamic responses that appear to be predictive of predisposition to cardiovascular disease in humans and rats. The possible applicability of the data from rat to a model for stress or cocaine-related cardiovascular disorders in humans will be determined by further analysis of responses in humans and rats. It is hoped that new risk factors may be identified using such a model, and that this model may facilitate predicting patients susceptible to cardiac disease and hypertension.

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