Increased susceptibility to ventricular arrhythmias in a rodent model of experimental depression

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Grippi, Angela J., Claudia M. Santos, Ralph F. Johnson, Terry G. Beltz, James B. Martins, Robert B. Felder, and Alan Kim Johnson. Increased susceptibility to ventricular arrhythmias in a rodent model of experimental depression. Am J Physiol Heart Circ Physiol 286: H619–H626, 2004;10.1152/ajpheart.00450.2003.—Depression is an important public health problem and is considered to be an independent risk factor for coronary artery disease. The pathophysiological mechanisms that link depression with adverse cardiovascular events (e.g., myocardial ischemia, myocardial infarction, and sudden death) are not well established. It is possible that an increased susceptibility to life-threatening cardiac arrhythmias in depressed patients influences the risk of morbidity and mortality in coronary artery disease. This idea was tested with the use of an experimental model of depression that was developed to induce anhedonia, the reduced responsiveness to pleasurable stimuli observed in human depressed patients. Rats exposed to 4 wk of chronic mild stress (e.g., paired housing, strobe light, and white noise) displayed anhedonia, which was operationally defined by the reduced intake of a palatable sucrose solution relative to an established baseline and to control animals. Furthermore, compared with control rats, the anhedonic rats showed increased basal heart rate and decreased heart rate variability. In response to an intravenously infused chemical challenge, aconitine, anhedonic rats exhibited an increased vulnerability to ventricular arrhythmias, as indicated by a reduced threshold for premature ventricular complexes, salvos, and ventricular tachycardia. These findings suggest that the presence of depressive symptoms is associated with a lower threshold for ventricular arrhythmias, which may contribute to the increased risk for adverse cardiovascular events in patients with depression.

Aconitine; animal models; chronic mild stress; coronary artery disease; electrocardiogram; heart rate variability; rats

Psychological depression is a common mood disorder that affects 2–3% of males and 5–9% of females at any single point in time (1). This condition is considered the leading cause of disability worldwide (quantified by years lived with a disease) and is exceeded only by coronary artery disease as the leading cause of disability in the United States (25). In addition to the impact that depression has on the population, this mood disorder is also considered a risk factor for coronary artery disease (8). The prevalence of depression in patients with coronary artery disease (e.g., myocardial infarction and heart failure) is ∼5 times that of the general population (37). Major depression is a significant predictor of mortality after myocardial infarction (8, 9). Its predictive ability on subsequent cardiovascular events, for example, myocardial infarction, arrhythmias, ischemia, or sudden cardiac death, is comparable to that of left ventricular dysfunction, previous myocardial infarction, and smoking (3, 8, 9). Perhaps even more important is the finding that depression is a significant risk factor for coronary artery disease in patients without a history of cardiovascular pathology. The risk of adverse cardiovascular events for depressed but otherwise healthy patients is similar to the risk for patients with established cardiovascular disease (31).

Several pathophysiological mechanisms have been proposed to influence the association between depression and coronary artery disease (see Ref. 13 for a recent review). These include 1) hypothalamic-pituitary-adrenal axis dysfunction associated with increased sympathetic activation (34); 2) an imbalance in parasympathetic and sympathetic inputs to the heart (i.e., increased sympathetic tone and/or decreased parasympathetic tone), manifest as reduced heart rate (HR) variability (5); and 3) altered serotonin activity affecting platelet function (28). It is also possible that the presence of depression may facilitate serious ventricular dysrhythmias. The presence of cardiac arrhythmias is an important precursor to mortality in patients both with and without cardiovascular disease (29, 41). Furthermore, a reduced threshold for ventricular fibrillation (VF) is proposed as the primary mechanism responsible for sudden cardiac death (44).

An important interaction between stress and ventricular arrhythmias has been noted. Several stressful environments have been shown to lower the threshold for VF in both the normal and acutely ischemic hearts of dogs (7, 23). Interestingly, depression appears to have an important interaction with stress in humans; in postmyocardial infarction patients, the presence of depression in combination with premature ventricular complexes (PVCs; >10 beats/h) greatly increases the likelihood of recurrent myocardial infarction (8). Because stressful life events have been suggested to be predisposing factors for depression (36) as well as predictors of the severity of depression (15), we have used a stress-induced animal model of depression to examine the influence of this disorder on ventricular arrhythmias. Chronic mild stress (CMS) is a rodent model of depression that was developed to mimic particular defining features of mood disorders, such as anhedonia (the reduced responsiveness to pleasurable stimuli) and reduced activity level (1, 49). Behavioral changes are induced via a combination of seemingly mild annoyances or stressors (e.g., strobe light, white noise, damp bedding, and paired housing) presented in an unpredictable manner. It has been
argued that the CMS model of depression has a high degree of predictive, face, and construct validity (46). Previously, we have shown elevated resting HR, reduced HR variability, exaggerated pressor and HR responses to a novel environmental stressor, and elevated sympathetic tone in rats exposed to 4 wk of CMS (11, 14). This animal model has also been used to study behavioral and physiological changes associated with depression (6, 10, 48), central nervous system mechanisms (27), and treatments for depressive disorders (17, 26).

In the present study, we have used the CMS model to examine a potential link between experimental anhedonia and the susceptibility to ventricular arrhythmias in rats. The current protocol employed a chemical challenge, aconitine, in rats exposed to CMS. Aconitine is arrhythmogenic in cardiac myocytes due to enhanced sodium influx into myocardial cells on both depolarization and repolarization and as a result of an increase in active Na⁺ current during depolarization (32). The utility of aconitine for the study of electrocardiographic activity is well documented. This drug has been used experimentally in anesthetized rats to investigate the vulnerability to ventricular arrhythmias as well as the efficacy of antiarrhythmic drugs (2, 18, 30, 40).

Previous work by Verrier and colleagues (7, 19, 21) and Skinner et al. (38, 39) has investigated the cardiac vulnerability in large animals, such as dogs and pigs, and has evaluated the effects of acute stressors that evoked short-lived emotional changes (e.g., akin to anger or fear). The study of ventricular function in the rat allows for testing hypotheses relating to behavioral changes associated with mood and physiological mechanisms of depression and cardiovascular function.

METHODS

Animals

Twenty-five male Sprague-Dawley rats (Harlan; Indianapolis, IN), weighing 300–400 g, were used for the experimental procedures. Rats were allowed 1 wk to acclimate to the surroundings before any experimentation began. Animals were housed in individual plastic cages with bedding. Food (Purina Rat Chow 5012) and tap water were available ad libitum for the duration of the experiments unless otherwise noted. Sucrose solution (1.0%) was available ad libitum for 1 wk before the experimental procedures to allow for adaptation to the taste of the sucrose. Sucrose was monitored daily to verify that all rats were consuming the solution. The temperature in the rat colony was maintained at 22 ± 2°C. The light cycle was held at 12:12 h, with lights on at 6 AM, unless otherwise noted. All procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the American Physiological Society’s “Guiding Principles for Research Involving Animals and Human Beings” and were approved by the University of Iowa Institutional Animal Care and Use Committee.

General Experimental Paradigm

The details for each procedure are described in Specific Experimental Procedures.

After adaptation to the animal colony, 13 of the rats were exposed to 4 wk of CMS and 12 of the rats were assigned to a control group. To operationally define anhedonia, sucrose preference tests were conducted before the onset of CMS and immediately after its termination. Three days after the CMS period, all rats were instrumented with a femoral vein catheter and two intramuscular recording electrodes. While under an Equithesin-like anesthetic, the rats were connected to a data-acquisition system for the electrocardiogram (ECG) recording. The anesthetized rats were tested for vulnerability to ventricular arrhythmias produced by an intravenous infusion of the arrhythmogenic drug aconitine.

Specific Experimental Procedures

CMS. In the CMS group, anhedonia was produced by the CMS protocol using a slight variation of methods described previously (11, 14). Briefly, the CMS group was exposed to the following mild stressors each week in random order: 1) continuous overnight illumination (two 12-h periods), 40° cage tilt along the vertical axis (one 7-h period); 2) paired housing (one 7-h period and one 48-h period); 3) soiled cage (300 ml of water spilled on bedding for one 12-h period); 4) exposure to an empty water bottle immediately after a period of acute water deprivation (17-h period of water deprivation and 1-h period of empty water bottle); 5) stroboscopic illumination (300 flashes/min; one 4-h period and one 6-h period); and 6) white noise (one 5-h period). The CMS procedure was carried out for a total of 4 wk. Control animals were left undisturbed in their home cages with the exception of routine handling (i.e., regular cage cleaning and measuring of body weight), which was matched to that of the CMS group.

Sucrose preference tests. Sucrose preference tests were employed to operationally define anhedonia. Anhedonia was specifically defined as a reduction in absolute sucrose intake and sucrose preference relative to a control group and preestablished baseline values. A sucrose preference test consisted of first removing the food and water (at 2 PM) from each rat’s cage for a period of 20 h. At 10 AM the next day, water and 1.0% sucrose were placed on the cages in preweighed glass bottles, and animals were allowed to consume the fluids for 1 h. The bottles were then removed and weighed. One preference test was conducted before beginning CMS (baseline) and one preference test was conducted after 4 wk of CMS.

Catheter and electrode preparation. Surgical procedures were conducted under an Equithesin-like anesthetic (composed of 0.97 g pentobarbital sodium and 4.25 g chloral hydrate/100 ml distilled water; 0.33 ml/100 g body wt; University of Iowa Hospital Pharmacy, Iowa City, IA) with the use of aseptic techniques. A polyethylene (PE-10 fused to PE-50) catheter was inserted into the abdominal vena cava via the left femoral vein. The catheter was filled with heparinized saline (200 U/ml). In a subset of rats, a second catheter was inserted into the aorta via the left femoral artery for the purpose of arterial pressure measurements. Immediately after this preparation, animals were implanted with two insulated wires (20 cm length, 2.03 mm internal diameter; lead II) for the recording of ECG. The skin was incised above the muscle in the right foreleg and the left hindleg. The wires were attached to the muscles with a nonabsorbable suture.

ECG testing and aconitine administration. ECG testing was performed while the rat was anesthetized immediately after the surgical preparation. Aconitine suppresses respiration and is toxic to cardiac myocytes (20, 35, 40); therefore, the animals were anesthetized rather than conscious. The rat was placed inside a grounded Faraday cage to shield electrical noise. The electrodes were connected to an ECG amplifier (Grass-Telefactor; W. Warwick, RI), which was attached to a PowerLab data-acquisition system (ADInstruments; Mountain View, CA). The analog input was acquired at a rate of 200 samples/s. Care was taken to ensure that each rat was anesthetized with a standardized dosage of an Equithesin-like anesthetic so that the level of respiration was similar across all animals. A measure of resting (baseline) ECG was recorded for 2–5 min.

All rats that participated in the behavioral tests were tested for arrhythmias in response to aconitine but were separated into two subgroups for the ECG tests. In one subset of rats (n = 5 CMS and 4 control), aconitine (Sigma Chemical, St. Louis, MO) was administered via constant intravenous infusion at a dose of 5 μg·kg⁻¹·min⁻¹ for 7–9 min. ECG activity was recorded continuously during drug infusion and for 2–5 min after discontinuation of the drug. The drug dosage
was chosen for its capacity to produce experimental ventricular arrhythmias in rats according to previously reported results (40). The first subgroup was used to determine a sufficient amount of aconitine to produce PVCs, and therefore only PVCs were recorded in these rats.

On the basis of the data recorded from the first subgroup of rats, the remaining rats in each group (n = 8 CMS and 8 control) were exposed to exactly 35 μg/kg of intravenous aconitine delivered at 5 μg·kg⁻¹·min⁻¹. ECG activity was recorded continuously during drug infusion and for 10–20 min after discontinuation of the drug. Because aconitine appears to be nonreversible without further intervention, anesthetized animals were euthanized with an overdose of pentobarbital sodium (50 mg/rat iv; Abbott Laboratories; Chicago, IL) at the end of the protocol.

Arterial pressure recordings. Arterial pressure was monitored in a subset of rats from each group (n = 3 CMS and 3 control rats). Catheters were connected to a pressure transducer (Maxxim Medical; Athens, TX) coupled to a multichannel recorder through a custom-designed amplifier for the recording of arterial pressure. The analog input was converted into a digital signal using a PowerLab data-acquisition system. This program permits sampling of hemodynamic data with a computer. Mean arterial pressure (MAP) was derived electronically using a low-pass filter, set at 100 Hz, and was calculated online using the cyclic mean. The sampling rate was 200 samples/s.

Data Analysis

Values are presented as means ± SE for the indicated analyses and figures. For all statistical tests reported herein, a probability value of P < 0.05 was considered to be statistically significant. Water and sucrose bottles from the 1-h sucrose preference tests were weighed to determine the amount of fluid consumed (in grams). Data from the preference tests were analyzed using mixed-design ANOVA (one factor for independent groups and one repeated-measures factor) and Student’s t-tests where appropriate. Body weight was statistically compared in CMS and control groups using Student’s t-tests.

Baseline electrocardiographic parameters were calculated from the data recorded before aconitine administration (baseline). HR was calculated from the raw data recording by measuring the number of heartbeats triggered from the ECG waveform using PowerLab data-analysis device. Mean values were statistically compared in CMS and control rats using Student’s t-test. An index of HR variability was calculated by taking the standard deviation of all R-R intervals (in ms) from the raw ECG waveform during a 2- to 5-min segment for each rat [SDNN index, as described by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (42)]. These segments of data were scored with a custom-designed macro. A mean SDNN index was calculated from these individual values and compared with the use of Student’s t-test. MAP was calculated from the arterial pressure waveform and compared with the use of Student’s t-tests. For blood pressure calculations, care was taken not to include any data during a period of changing or unstable blood pressure. For HR and HR variability calculations, care was taken not to include data during periods of unstable HR.

Classification of arrhythmias was based on the Lambeth Conventions (45; see Table 1). Six classes of arrhythmias were determined for each rat: none (normal rhythmic activity with a P wave), PVC, premature ventricular complex (premature with respect to the P wave), bigeminy (a series of two PVCs for each P wave), ventricular tachycardia (VT; a run of four or more premature QRS complexes), ventricular fibrillation (VF; no discernable rhythm, with QRS complexes not corresponding with PVC, premature ventricular complex. See Ref. 45 for details about Lambeth conventions.

### Table 1. Classes of arrhythmias according to Lambeth Conventions

<table>
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<tr>
<th>Convention</th>
<th>Definition</th>
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<tr>
<td>Isolated ventricular premature beat/PVC</td>
<td>A discrete and identifiable premature QRS complex (premature with respect to the P wave).</td>
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<tr>
<td>Bigeminy</td>
<td>A variant of ventricular premature beats characterized by the following minimum sequence: P, QRS, PVC, P, QRS, PVC.</td>
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<tr>
<td>Salvo</td>
<td>Two or three premature QRS complexes.</td>
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<tr>
<td>Ventricular tachycardia</td>
<td>A run of four or more premature QRS complexes; not to be defined in terms of its rate or the prevailing sinus rate.</td>
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<tr>
<td>Ventricular fibrillation</td>
<td>A signal for which individual QRS deflections can no longer be distinguished from one another and for which a rate can no longer be measured.</td>
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PVCs were calculated for all rats. In the subset of rats that received an equal dose of aconitine (35 μg/kg at 5 μg·kg⁻¹·min⁻¹), the time required for the onset of bigeminy, salvos, VT, and (when applicable) VF was calculated. ECG data were compared in CMS versus control groups using Student’s t-tests.

RESULTS

Sucrose Preference Tests and Body Weight

Figure 1 displays the percent preference for sucrose in CMS and control groups at baseline and after 4 wk of CMS. Figure 1A presents absolute water and sucrose intake in the two groups. Mixed-design ANOVAs were performed separately for water and sucrose intake. No significant differences in water intake were found. An ANOVA performed on sucrose intake yielded a main effect of time, main effect of group, and a group by time interaction. There was no difference in sucrose intake between the two groups at baseline. After 4 wk of CMS, the CMS group consumed significantly less sucrose than the control group and its respective baseline value.

Figure 1B displays the percent preference for sucrose in CMS and control groups at baseline and after 4 wk of CMS. The percent preference for sucrose was calculated according to the following formula: %preference = (sucrose intake/total fluid intake) × 100. An ANOVA yielded a main effect of group. The baseline preference for sucrose did not differ between CMS and control animals. However, after 4 wk of CMS, the preference for sucrose was reduced in the CMS group compared with its respective baseline value and that of the control group.

Body weight was statistically compared in CMS and control rats with an ANOVA. As expected, there was a main effect of time, but there was no main effect of group and no group by time interaction. Body weight during the baseline period was 322.7 ± 4.1 g in CMS rats and 323.5 ± 3.7 g in control rats, and after 4 wk of CMS, body weight was 396.4 ± 5.6 g in CMS rats and 393.6 ± 5.0 g in control rats. The two groups did not statistically differ in body weight at either of these time points.
Baseline Electrocardiographic Parameters

Data recorded before aconitine administration (baseline) were analyzed for HR and HR variability. The CMS group demonstrated significantly elevated HR compared with the control group (Fig. 2A). HR variability (SDNN index) was significantly reduced in the CMS group relative to the control group (i.e., the CMS group displayed a reduced threshold for isolated PVCs). Isolated PVCs were typically the only arrhythmic event present during 7 min of aconitine infusion; therefore, a subset of rats was exposed to 35 μg/kg of aconitine at 5 μg·kg⁻¹·min⁻¹ for the purpose of observing more complex arrhythmias that take place after discontinuation of the drug. Figure 5 presents the time required for the onset of bigeminy, salvo, VT, and VF in this subset of rats. Rats exposed to CMS displayed a reduced threshold for salvo and VT in response to aconitine administration. The time required for the onset of salvo (n = 6 CMS and 6 control) and VT (n = 8 CMS and 5 control) was significantly reduced in the CMS group relative to control rats. The time required for the onset of bigeminy (n = 7 CMS and 7 control) was not significantly different between the two groups.

Aconitine Administration

Experimental ventricular arrhythmias were classified into the following categories: isolated PVC, bigeminy (bigeminal PVCs), salvo, VT, and VF. Figure 3 displays the raw data recording from a representative rat showing each category of arrhythmia. Not all rats demonstrated a stepwise progression through these stages and some rats did not display certain types of arrhythmic events during the ECG recording period. Therefore, statistical analyses were performed on those rats that displayed similar types of ventricular arrhythmias. Atrial events were not used in the statistical comparisons. Sample sizes are noted for all statistical tests.

Figure 4 presents the PVC data for 11 CMS and 11 control rats, showing the time required for aconitine to produce the onset of isolated PVCs. The mean latency for the onset of PVCs, and hence the total drug dosage administered (10.6 ± 1.2 μg in CMS vs. 13.0 ± 1.1 μg), was significantly reduced in the CMS group relative to the control group (i.e., the CMS group displayed a reduced threshold for isolated PVCs). Isolated PVCs were typically the only arrhythmic event present during 7 min of aconitine infusion; therefore, a subset of rats was exposed to 35 μg/kg of aconitine at 5 μg·kg⁻¹·min⁻¹ for the purpose of observing more complex arrhythmias that take place after discontinuation of the drug. Figure 5 presents the time required for the onset of bigeminy, salvo, VT, and VF in this subset of rats. Rats exposed to CMS displayed a reduced threshold for salvo and VT in response to aconitine administration. The time required for the onset of salvo (n = 6 CMS and 6 control) and VT (n = 8 CMS and 5 control) was significantly reduced in the CMS group relative to control rats. The time required for the onset of bigeminy (n = 7 CMS and 7 control) was not significantly different between the two groups.
Arterial Pressure Recordings

In a subset of rats, arterial pressure was recorded via a catheter in the left femoral artery. These measurements were taken concurrently with the ECG recordings. Baseline (pre-aconitine) MAP was 80.4 ± 3.5 mmHg in the CMS group and 79.0 ± 2.6 mmHg in the control group; these values were not significantly different. Administration of aconitine reduced MAP in all rats (CMS and control groups). Figure 6 presents MAP in CMS and control groups at baseline and at significant time points during aconitine infusion. During aconitine infusion but before the onset of the first arrhythmic event, MAP was significantly higher in the CMS group than the control group. However, there was no significant difference in MAP between CMS and control groups immediately preceding the onset of the first arrhythmic event (e.g., blood pressure during 1 min immediately before the first isolated PVC). Immediately before VT, MAP was significantly higher in the control group versus the CMS group, but there was no significant difference in MAP during the time that immediately preceded VF. Furthermore, MAP was not different between the two groups either during VT or during VF (data not shown).

DISCUSSION

The current study was undertaken to determine whether rats with CMS-induced anhedonia (i.e., experimental depression) were more susceptible than control rats to experimentally induced cardiac arrhythmias. Both behavioral and cardiovascular changes were observed in rats exposed to CMS. CMS appears to produce a reduced threshold for ventricular arrhythmias that may signal an increased risk of detrimental cardiovascular outcomes (e.g., myocardial infarction, heart failure, and sudden cardiac death).

Similar to previous investigations (14, 50), sucrose intake was significantly reduced in rats exposed to 4 wk of CMS in
a reduced threshold for specific ventricular arrhythmias after theourth week of CMS exposure. Isolated PVCs appeared significantly
earlier (and therefore with less aconitine) in CMS rats compared
with control rats. Likewise, the time required for onset of salvos and
VT was significantly reduced in the CMS group. The reduced
threshold for arrhythmic events associated with CMS appears to
have not only statistical significance but also clinical relevance.
The onset of PVCs occurred 20\% earlier, whereas salvos and VT
occurred 17\% and 23\% earlier, respectively, in CMS rats compared
with control rats suggesting that CMS is associated with important
ventricular disturbances. However, it is possible that ventricular
function is differentially altered in CMS and control animals
under anesthesia, and thus it would also be beneficial to investigate
ECG activity in conscious rats.

Aconitine may also affect blood pressure, thereby indirectly
influencing cardiac rhythm via stress on the left ventricle. In
the present study, baseline blood pressure was similar in the
CMS and control groups. During aconitine infusion (before the
first arrhythmic event), MAP was lower in the control group
than in the CMS group. However, when MAP was calculated
immediately preceding the first isolated PVC, it was not
significantly different in CMS and control groups. MAP was
also similar in the two groups immediately preceding VF,
during VT, and during VF. The similarities of blood pressure
in CMS and control groups both at baseline and during ar-
rhymic events suggest that changes in arterial pressure do not
modulate changes in ECG. On a related note, Lown and
colleagues (22) have suggested that changes in HR and blood
pressure are not necessary for changes in cardiac excitability.

The present study provides an important step in the mech-
nanistic analysis of the nature of cardiovascular disease that
accompanies a key component of psychological depression,
anhedonia. Rats exposed to CMS show an increased vulnera-
bility to ventricular arrhythmias in an experimental paradigm,
which supports the hypothesis that the association between
depression and heart disease involves an arrhythmic mecha-
nism (9). The cardiac arrhythmias observed in the present
study were of several varieties, including isolated PVCs as well
as more complex tachycardia. It is possible that the generation
of these abnormalities in CMS rats is a result of inappropriate
impulse formation from the sinus node or a problem with
impulse conduction due to reentrant mechanisms (16, 51). The
data from the present investigation complement our previous
finding that rats exposed to CMS display elevated sympathetic
cardiac tone, which mediates HR and HR variability in these
animals (14). Increased sympathetic activity predisposes the
heart to ventricular arrhythmias, and may influence the ectopic
activity that precedes VF (22, 43). Thus it is possible that
altered autonomic tone, in particular elevated sympathetic tone,
plays a role in the susceptibility to arrhythmic events observed
in the present study. Furthermore, the central nervous system
pathways that affect sympathetic outflow to the cardiovascular
system may also be altered in CMS, in turn increasing the risk
of cardiac arrhythmias (41).

Further investigations should focus on determining the cen-
tral nervous system mechanisms that are driving the changes in
sympathetic tone and susceptibility to cardiac arrhythmias
in the CMS model. It might be interesting to also examine the
susceptibility to arrhythmias in CMS rats that were allowed to
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study from our laboratory (11), which showed elevated resting HR and reduced resting HR variability in CMS rats that were tested 4 wk after discontinuation of the CMS procedure, one might predict that the susceptibility to cardiac rhythm disturbances would similarly persist beyond the recovery of behavioral alterations.

The current study extends the findings from previous investigations of stress and cardiac function by providing additional insight regarding the nature of cardiovascular function in a rodent model of psychological depression as defined by the presence of anhedonia. Furthermore, these data complement a previous study from our laboratory showing that experimental heart disease (congestive heart failure) induces anhedonia in rats (12). Whereas previous work (7, 19, 21, 23, 38, 39) has focused on cardiac vulnerability during or after acute stressors, the present investigation examined the susceptibility to ventricular arrhythmias in the presence of anhedonia after a prolonged period of exposure to mild stressors. In addition, these methods were conducted in the rat, providing a foundation for systematically evaluating behavioral and physiological influences on cardiovascular regulation and the role that the nervous system plays in these associations. The use of controlled experimental methods, such as those employed here, may shed light on the mechanisms that underlie the increased risk for coronary artery disease in individuals with mood disorders, and may aid in the development of beneficial treatments for these patients.

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REFERENCES


