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Vulnerability to arrhythmias during social stress in rats with different sympathovagal balance

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Sgoifo, Andrea, Siets F. de Boer, Bauke Buwalda, Gerdien Korte-Bouws, J olanda Tuma, Bela Bohus, Johan Zaagsma, and Jaap M. Koolhaas. Vulnerability to arrhythmias during social stress in rats with different sympathovagal balance. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H460–H466, 1998.—An increased activity of the sympathetic nervous system is an important factor in the genesis of ventricular arrhythmias. Changes in average R-R interval, R-R interval variability (indirect measure of sympathovagal balance), occurrence of arrhythmias, and plasma norepinephrine concentrations were measured during a social stress episode (defeat) in two strains of rats, Wistar and wild type, which were supposed to differ in their autonomic stress responsiveness. Electrocardiograms were telemetrically recorded, and blood samples were withdrawn through jugular vein catheters from healthy, freely moving animals. R-R interval variability was estimated by the following time-domain parameters: the standard deviation of the mean R-R interval, the coefficient of variance, and the root mean square of successive differences (r-MSSD) (5, 21, 23). The information obtained with these parameters has been shown to correlate well with frequency-domain measurements of R-R interval variability (21). SD and SD/RR, which provide the same information given by the total power of the spectrum of R-R interval variability, are both measures of the total variance in the heart rate signal. They provide an overall estimation of the balance between autonomic balance and risk of arrhythmias.

ECGs were recorded by means of a telemetry system, which allows reliable measurements during agonistic interactions between the animals (15, 18). Information on autonomic control of the heart was obtained using time-domain measurements of heart rate variability, namely the standard deviation of the average R-R interval (SD), the coefficient of variance (i.e., the ratio SD/RR, where RR is the mean R-R interval duration), and the root mean square of successive R-R interval differences (r-MSSD) (5, 21, 23). The information obtained with these parameters has been shown to correlate well with frequency-domain measurements of R-R interval variability (21). SD and SD/RR, which provide the same information given by the total power of the spectrum of R-R interval variability, are both measures of the total variance in the heart rate signal. They provide an overall estimation of the balance between autonomic balance and risk of arrhythmias.

An increased sympathetic activity, as induced by a number of stressful conditions, can lower the threshold for severe cardiac arrhythmias, whereas the predominance of vagal modulation is generally linked to a reduced incidence of ventricular events. This association has been demonstrated mainly in clinical case reports and animal experiments in which an underlying altered cardiac substrate was present, such as coronary artery disease, myocardial hypertrophy, and/or heart failure (9, 12, 25, 27).

On the other hand, little information is available on the relationship between stress-induced changes of autonomic balance and vulnerability to arrhythmias in animals with no evident cardiovascular pathology. In this regard, we recently documented the impact of different stressful situations on the cardiac electrical activity of normal wild-type rats (14). A social stressor like defeat was shown to induce a marked shift of autonomic balance toward the sympathetic branch, which was accompanied by the occurrence of ventricular arrhythmias, whereas a nonsocial challenge like restraint was characterized by a strong vagal recruitment and a negligible incidence of ventricular extrasystoles.

However, it still remains to be proven whether, within the same stress condition, healthy animals with a higher incidence of ventricular arrhythmias also show a lower heart rate variability. The aim of the present study was therefore to provide further evidence for the association between sympathetic predominance and vulnerability to ventricular ectopic events in young adult rats exposed to a brief social stress experience (14). For this purpose, we compared electrocardiographic (ECG) responses (i.e., changes in heart rate, heart rate variability, and incidence of arrhythmias) to social defeat in two different strains of rats, Wistar and wild type, which were supposed to differ in their autonomic reactivity to stress. In fact, some indications have been provided of a higher heart rate response and a larger incidence of ventricular arrhythmias in a wild-type strain of rats compared with Wistar rats during acute social stress (17). Moreover, plasma catecholamine determinations also indicated that wild-type animals react to such a challenging situation with a much higher sympathoadrenomedullary activation compared with Wistar rats (13, 16). Therefore, these two strains may be viewed as extremes, as far as sympathovagal balance is concerned, within the range of the natural variation of this species, thus representing a good model for testing the relationship between autonomic balance and risk of arrhythmias.

Telemetry electrocardiograms; autonomic nervous system; norepinephrine; defeat; vagal tone
sympathetic and parasympathetic activities on the heart. The r-MSSD, which correlates highly with the high-frequency power of the spectrum, more specifically quantifies the vagal influence on heart rate variability (21). An indirect estimation of the sympathetic input to the heart during social stress in the two strains of rats was also obtained, via determination of plasma norepinephrine (NE) concentrations.

METHODS

All procedures in this study were approved by the Committee on Animal Bioethics of the University of Groningen, Groningen, The Netherlands.

Animals and Housing

We used 24 Wistar and 24 wild-type male rats (Rattus norvegicus). Wistar rats were obtained from Charles River Benelux (originally derived from TNO/CPB) and locally bred at the Department of Animal Physiology, University of Groningen, The Netherlands. Wild-type rats were originally derived from the Agricultural University of Wageningen (Wageningen, The Netherlands) and bred in our department under conventionally clean conditions. The wild-type animals used in these experiments belonged to the 20th generation of laboratory breeding.

Animals were housed in unisexual groups of four individuals, from weaning until the onset of experiments (6 mo of age), in clear Plexiglas cages measuring $60 \times 40 \times 20$ cm. Additional males were used as resident dominants in the social stress test (resident-intruder test; see Social Stress for details). Each resident was permanently housed with a female in a wooden cage (85 $\times$ 60 $\times$ 50 cm) in order to induce and preserve high levels of aggression toward strange male conspecific intruders (7). Experimental and dominant males were kept in separate rooms with controlled temperature (22 $\pm$ 2°C) and lighting (lights on from 2000 to 0800). The bedding of the cages consisted of wood shavings, and food and water were freely available.

Telemetry System

The telemetry system used in this study consisted of a flat transmitter measuring $25 \times 15 \times 8$ mm (TA11CTA-F40, Data Sciences International, St. Paul, MN) and a platform receiver measuring $74 \times 47 \times 3$ cm, manufactured by the Electronic Department in the Biological Center of the University of Groningen (Haren, The Netherlands).

Surgeries

Transmitter implantation. In 16 Wistar and 16 wild-type rats, the telemetry ECG transmitter was chronically implanted following a surgical procedure that also guarantees high-quality ECG recordings during sustained physical activity (18). Briefly, the body of the transmitter is placed into the abdominal cavity, and the two electrodes (wire loops) are fixed to the dorsal surface of the xiphoid process and in the anterior mediastinum close to the right atrium.

Jugular vein cannulation. The remaining 16 males (8 Wistar and 8 wild type) were provided with a Silastic heart cannula (1 D 0.5 mm, OD 0.9 mm; Dow Corning) through the right jugular vein, with one end reaching the entrance of the right atrium and the other one externalized on top of the skull, according to the technique originally described by Steffens (20). This method allows frequent blood sampling in freely behaving rats, even in conditions of overt fighting between the opponents (13).

Surgeries were performed under halothane anesthesia (Fluothane, Zeneca, Ridderkerk, The Netherlands). Subsequently, rats were prophylactically injected with penicillin (Natrium-penicillin G, 40,000 IU/kg body wt sc; Yamanouchi, Leiderdorp, The Netherlands) and individually housed in clear Plexiglas cages measuring $25 \times 25 \times 30$ cm.

Social Stress

The social stress test was performed 10 days after ECG transmitter or jugular vein cannula implantation. Each recording session consisted of baseline, test, and recovery periods lasting 15 min each. One hour before baseline, either the telemetry transmitter was switched on or a long polyethylene tube was connected to the externalized end of the catheter for blood withdrawal. During baseline, experimental animals were left undisturbed in their own home cages. Subsequently, Wistar rats (among which 16 bearing the ECG transmitter and 8 bearing the jugular cannula) and wild-type rats (16 bearing the ECG transmitter and 8 bearing the jugular cannula) were individually introduced into the home cage of a highly aggressive resident (trained fighter) after temporary removal of the female partner (resident-intruder test), where they were vigorously attacked (1). From telemetered rats, ECGs were continuously recorded during baseline, test, and recovery periods. From cannulated rats, blood samples of 0.5 ml were withdrawn at minutes 5 and 15 of baseline and minutes 1, 5, and 15 of the test. To measure the recovery of basal NE levels, we also took blood samples 15 and 45 min after test termination, with the animal back in its home cage. After each sample, the same amount of donor blood was transfused through the catheter to avoid changes in hemodynamics. Donor blood was obtained from additional unstressed rats provided with permanent heart catheters. All experimental sessions were performed in the dark phase between 10:00 AM and 1:00 PM.

ECG Data Acquisition and Processing

The pulse-modulated signal at the output of the receiver was simultaneously routed to two IBM-compatible personal computers (PC). One PC was provided with a software package developed in our laboratory (CARDIA) for real-time acquisition and analysis of R-R intervals. R waves were converted into pulses using a threshold circuit. Pulse times were measured with $<0.5$-ms accuracy. R-R pulse intervals were expressed as heart rate (beats/min), displayed on-line, and stored for subsequent analysis. The second PC contained LABPRO data-acquisition system (Data Sciences), which was used only for monitoring, storage, and visual inspection of ECG waves. The following ECG parameters were quantified: 1) the mean R-R interval duration (ms); 2) the variability of R-R interval measured in the time domain and expressed in three forms: SD (ms), the coefficient of variance (SD/RR) (5), and the r-MSSD (ms) (21); and 3) the number of the most common arrhythmic events, such as ventricular premature beats and second-degree atrioventricular blocks (3, 14). Whereas SD and SD/RR estimate the overall heart rate variability and therefore include the contribution of both branches of the autonomic nervous system to heart rate control, the r-MSSD specifically quantifies the influence on heart rate variability of the parasympathetic input to the heart (21, 23). Mean R-R interval duration and R-R variability measures were performed after removal of R-R intervals surrounding arrhythmias.
Determination of NE Concentrations

Blood samples were immediately transferred to chilled (0°C) centrifuge tubes containing EDTA and 10 μl heparin solution (500 IU/ml). Blood was centrifuged at 5°C for 10 min at 2,600 rpm, and 100 μl of the supernatant were stored at −80°C. Determination of plasma NE concentrations was performed by means of HPLC in combination with electrochemical detection, according to the technique described by Smedes and colleagues (19).

Statistical Analysis

Quantification of aggressive interactions during the resident-intruder test was limited to the number of attacks received by each intruder and the latency (in s) to first biting attack. For both parameters, comparison between the two strains was performed by means of one-way ANOVA.

From the ECG recordings, R-R interval parameters (mean R-R interval duration, SD, SD/RR, and r-MSSD; see ECG Data Acquisition and Processing) were quantified as means of 15- or 3-min periods for all recording conditions (baseline, test, and recovery). Means of 15-min periods were compared via one-way ANOVA, whereas comparisons of means of 3-min periods between Wistar and wild-type animals were performed using two-way ANOVA, with rat strain as between-subject factor (2 levels) and time as repeated-measures within-subject factor (11 levels). The occurrence of various kinds of arrhythmias was expressed as the number of events per each 15-min recording period (baseline, test, and recovery). For each cannulated animal, the two baseline measurements of NE were averaged, and only mean values were used for statistical analysis. The response patterns of NE were first evaluated using a two-way ANOVA, with rat strain as between-subject factor (2 levels) and sampling time as repeated-measures within-subject factor (6 levels). Plasma NE responses were also quantified by computing the area under the response time curve (AUC) above the baseline. The AUC values were statistically analyzed by means of a one-way ANOVA. Further post hoc analyses on ECG and humoral data were performed by means of Scheffe’s test. Values for ECG parameters together with plasma levels and AUC values for NE and behavioral patterns were expressed as means ± SE. Statistical significance was set at P < 0.05.

RESULTS

Aggressive Interactions During Defeat

During the 15-min resident-intruder test, Wistar and wild-type intruders received, respectively, 17.4 ± 2.3 and 17.3 ± 1.4 attacks. The mean latency time to first biting attack was 21.1 ± 4.9 and 19.9 ± 3.9 s, respectively. Therefore, the amount of aggression received by the intruders of the two strains was very similar (no statistically significant differences; 1-way ANOVA). Moreover, in both cases the aggressive behavior toward the intruders was exhibited by the dominants throughout the test duration and was independent of the type of implantation (transmitter or cannula).

ECG Responses

Average R-R interval and R-R interval variability. In both strains, 15-min-period mean R-R interval values were significantly decreased during social defeat compared with baseline, and they were still significantly lowered in the recovery phase (Wistar: baseline = 197.7 ± 4.6 ms, test = 128.2 ± 1.9 ms, recovery = 149.9 ± 2.1 ms; wild type: baseline = 165.6 ± 3.1 ms, test = 115.8 ± 0.8 ms, recovery = 134.3 ± 2.5 ms; P < 0.01). However, values of R-R interval were significantly lower in wild-type rats in baseline as well as in the test and recovery periods (P < 0.01). R-R variability, measured as SD of the mean of 15-min periods, was significantly decreased during defeat compared with baseline both in Wistar and wild-type rats (Wistar: baseline = 9.7 ± 0.8 ms vs. test = 7.1 ± 0.7 ms, P < 0.05; wild type: baseline = 10.4 ± 0.7 ms vs. test = 3.8 ± 0.2 ms, P < 0.01). However, whereas SD was back to baseline in wild-type rats during recovery (10.6 ± 1.1 ms), it was further increased in Wistar rats (15.3 ± 0.9 ms, P < 0.01). In addition, test and recovery values were significantly lower in wild-type compared with Wistar rats (P < 0.01), whereas starting pretest values were similar.

R-R variability expressed as SD corrected by heart rate (SD/RR) was unchanged during defeat in Wistar rats (baseline = 0.049 ± 0.005, test = 0.054 ± 0.01) but markedly decreased in wild-type rats (baseline = 0.063 ± 0.004 vs. test = 0.033 ± 0.001, P < 0.01). During recovery, SD/RR markedly increased in Wistar rats (0.102 ± 0.006, P < 0.01), but it was not significantly different from baseline in wild-type animals (0.077 ± 0.006). As for SD, the coefficient of variance was lower in wild-type compared with Wistar rats in both test and recovery periods (P < 0.01) and tendentially lower in baseline (P = 0.053). Values of the r-MSSD, which specifically quantifies the short-term components of R-R interval variability (parasympathetic input to the heart), were only slightly increased in Wistar rats across the recording session (baseline = 2.82 ± 0.33 ms, test = 2.97 ± 0.39 ms, recovery = 3.14 ± 0.29 ms). In contrast, in wild-type rats the r-MSSD was significantly reduced during defeat and recovery (test = 1.89 ± 0.08 ms, recovery = 2.37 ± 0.22 ms; P < 0.01 and P < 0.05, respectively, vs. baseline = 3.38 ± 0.38 ms). Also, Δ values (increment at test compared with baseline) for mean R-R interval duration, SD, SD/RR, and r-MSSD were significantly different between Wistar and wild-type intruders (R-R interval: F = −2.9; SD: F = 3.5; SD/RR: F = 4.9; r-MSSD: F = 2.5; 1-way ANOVA: P < 0.05).

Figure 1 shows a more detailed picture of the time-evolution of R-R interval and R-R interval variability measures during social stress in the two strains of rats. Mean values were calculated for each 3-min time period in which the test and recovery phases were divided. Wild-type rats had lower values of average R-R interval compared with Wistar counterparts in baseline conditions (t = 0) and across all the test and recovery periods (from t = 3 min to t = 30 min) (P < 0.01; Fig. 1A). Values of SD, SD/RR, and r-MSSD (Fig. 1, B-D, respectively) were similar in the two strains in the 3 min preceding the stress exposure (t = 0 min in Fig. 1), but they were significantly lower in wild-type compared with Wistar rats throughout the test and recovery periods (P < 0.05; with the exceptions of t = 27
min for SD, t = 21, 27, and 30 min for SD/RR, and t = 9, 27, and 30 min for r-MSSD).

Arrhythmias. Figure 2 reports examples of the most common arrhythmic events recorded in Wistar and wild-type rats during and after stress exposure. During the test, ventricular premature beats (VPB, either isolated or as couplet or triplet; Fig. 2B) were far more recurrent than any other kind of arrhythmia in both strains. The incidence of VPB during defeat was much higher in wild-type compared with Wistar rats (30.6 ± 4.2 vs. 9.2 ± 2.7, P < 0.01; Fig. 2D). The most frequent arrhythmic events observed during recovery were second-degree atrioventricular blocks (Fig. 2C), with no significant differences between strains (4.7 ± 1.7 vs. 6.7 ± 1.9, F = 0.7; Fig. 2D).

**Plasma NE Levels**

Figure 3 shows the mean time course of plasma venous concentrations of NE during social stress in Wistar and wild-type rats. In both strains, the stressor induced significant increments of NE compared with baseline, which lasted until the end of recovery (P < 0.01 for wild-type and P < 0.05 for Wistar rats).

Maximum peak values were found at t = 1 min for Wistar rats (1,174 ± 178 pg/ml) and t = 5 min for wild-type rats (2,594 ± 472 pg/ml). NE plasma concentrations were much higher in wild-type compared with Wistar rats during baseline, as well as during the test and recovery periods (P < 0.01; except for t = 1 min, P < 0.05).

A quantitative overall comparison between the two strains was obtained by using the AUC above baseline during the test and recovery periods. Stress-induced elevations of plasma NE were much higher in wild-type compared with Wistar rats (42,784 ± 6,324 and 12,757 ± 2,425 pg·min⁻¹·ml⁻¹, respectively; F = 13.5, P < 0.01).

**DISCUSSION**

The acute ECG and plasma NE responses to a social stressor (defeat) were studied in Wistar and wild-type healthy rats. Average R-R interval and R-R interval variability measures, as well as plasma NE concentrations, indicated a higher sympathetic tone, a higher sympathetic responsiveness, and a lower parasympathetic antagonism after the sympathetic activation in wild-type animals, which also showed a much higher incidence of ventricular arrhythmias. This association highlights the role of a marked shift of autonomic balance toward the sympathetic component in the occurrence of ventricular arrhythmias, even in the absence of evident cardiovascular pathologies (14).

In baseline conditions, the lower R-R interval values and the higher concentrations of plasma NE of wild-type rats suggest that they are characterized by a higher sympathetic tone compared with Wistar rats, whereas measurements of R-R interval variability (especially the r-MSSD) indicate that there are no significant differences between the strains in terms of basal parasympathetic activity.

Under challenging conditions (social defeat), the two strains reacted with a substantially different pattern of autonomic response. Although both groups of animals showed a marked increase of heart rate and plasma NE concentrations (13, 16, 17), values of these parameters were always significantly higher in wild-type rats compared with Wistar counterparts. Moreover, whereas Wistar rats showed no significant change in autonomic balance (SD and SD/RR measures) and no significant reduction of parasympathetic activity (r-MSSD) across the test period, wild-type animals had all these parameters significantly decreased compared with basal conditions, suggesting a marked shift of the autonomic
Interestingly, wild-type animals were characterized by little variation in individual response during the test, as suggested by low values of the SE for all ECG parameters. On the other hand, previous experimental evidence pointed out a high individual variability in catecholaminergic stress reactivity in the same strain of rats (13). Therefore, we believe that the ECG stress response described here might have been close to its physiological maximum.

In the posttest recovery phase, not only were heart rate variability measures still significantly lower in wild-type compared with Wistar rats, but they again indicated a qualitatively different pattern of autonomic response. In Wistar rats, heart rate variability measures were significantly (SD and SD/RR) or tendentially (r-MSSD) enhanced in this phase compared with baseline, whereas they were back to baseline (SD and SD/RR) or still significantly lowered (r-MSSD) in wild-type rats. In other words, whereas Wistar rats show a remarkable vagal recruitment in the period of time just after stress exposure, wild-type counterparts only show a poor parasympathetic rebound after sympathetic stimulation.

The use of time-domain measurements of heart rate variability as a tool to evaluate the autonomic input to the heart is not entirely free from limitations, especially when applied to short-term recordings. The main limit of these statistical methods is that they provide more qualitative than quantitative information. On the other hand, power spectral analysis of heart rate variability may provide more detailed information regarding the relative contribution of the two branches of the autonomic nervous system (23). However, time- and frequency-domain measures are tightly related, i.e., for every frequency-domain measure there is a time-domain measurement that strongly correlates with it ($R > 0.85$) (21). The r-MSSD in particular is so closely correlated with the high-frequency power of heart rate variability that, for all practical purposes, it is interchangeable with the spectral measure (22). In addition, as pointed out by Lombardi and colleagues (8), despite...
the impressive growth of research in the field of frequency-domain measurements, the most rewarding clinical results in the field of prognosis have so far been obtained with the time-domain indexes.

The incidence of arrhythmias during the test also supports this view of a different “autonomic behavior” in the two strains. Ventricular arrhythmias (ventricular premature beats, as isolated events or as couplets or triplets), which were monitored mostly during the test period, were approximately fourfold more frequent in wild-type rats. The association of higher heart rate variability and lower incidence of ventricular arrhythmias during defeat in Wistar rats is in accordance with the generally accepted view of a protective role against arrhythmia vulnerability exerted by the vagal component of the autonomic input to the heart (10, 24, 26).

These data demonstrate that a quantitatively significant occurrence of ventricular arrhythmias (though not, of course, of the malignant type, such as sustained ventricular tachycardia or fibrillation) can be induced in young adult rats with no underlying cardiovascular pathology. Moreover, this induction can be obtained with a simple, short-term naturalistic/physiological challenge such as social defeat (6, 17). The standardization of such a behavioral test for measuring autonomic stress responses can be questioned, as it is not as easy to achieve compared with other environmental (e.g., restraint or shock prod) (4, 11) or pharmacological challenges. However, the amount of aggression received by the experimental animals of the two strains, measured as the number of attacks and the latency time to first biting attack by the aggressive resident, was very similar. Moreover, no significant correlation was found between the number of attacks received (or the rapidity of the aggressive interaction onset), which differed from animal to animal, and the recorded changes in cardiac electrical activity.

A reliable ECG recording during such an aversive situation can be successfully achieved only by using a chronically implantable telemetry system, which does not limit the aggressive interactions between the opponents (2, 15), and by locating the ECG transmitter leads far from major skeletal muscle layers, whose significant electrical activity during aggressive confrontation would otherwise greatly affect the recordings (18).

In our study, ECG and neuroendocrine responses were measured in different groups of animals. Although this precluded direct correlations between individual plasma NE and heart rate and arrhythmia responses, uncontrollable effects of blood sampling/donation maneuvers on hemodynamics and consequently on ECG measurements (e.g., baroreflexes) were prevented. Nevertheless, a general association between the level of cardiac sympathetic activation, as indirectly measured by plasma NE determinations, and the occurrence of rhythm disturbances was clearly found. Wild-type rats, in which social defeat provoked a much higher incidence of ventricular ectopic beats compared with their Wistar counterparts, were also characterized by much higher plasma NE levels.

In conclusion, Wistar rats appeared to have a lower baseline sympathetic tone, a lower sympathetic reactivity to stress, and a much higher parasympathetic counterreactivity to sympathetic activation compared with wild-type subjects. Accordingly, they also showed a much lower incidence of ventricular ectopic beats during the test, as well as a slightly higher occurrence of second-degree atrioventricular blocks during post-test recovery period. Although these relationships were obtained using two different strains of rats, this was meant to represent a first step in the attempt to prove, also in subjects without underlying cardiovascular pathology, the association between individual rate of ventricular arrhythmias and sympathetic predominance during social stress episodes.

The comparison between these two strains might also represent a useful experimental model for studying in more detail the mechanisms (cellular/electrophysiological) responsible for the vulnerability to arrhythmias in healthy individuals exposed to stressful situations.

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