Chewing reduces sympathetic nervous response to stress and prevents poststress arrhythmias in rats

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Koizumi S, Minamisawa S, Sasaguri K, Onozuka M, Sato S, Ono Y. Chewing reduces sympathetic nervous response to stress and prevents poststress arrhythmias in rats. Am J Physiol Heart Circ Physiol 301: H1551–H1558, 2011. First published August 5, 2011; doi:10.1152/ajpheart.01224.2010.—Reducing stress is important in preventing sudden death in patients with cardiovascular disease, as stressful events may cause autonomic imbalance and trigger fatal arrhythmias. Since chewing has been shown to inhibit stress-induced neuronal responses in the hypothalamus, we hypothesized that chewing could ameliorate stress-induced autonomic imbalance and prevent arrhythmias. To test this hypothesis, we analyzed changes in radiotelemetered electrocardiograms in rats that were allowed to chew a wooden stick during a 1-h period of immobilization stress. Chewing significantly reduced the occurrence of ventricular premature beats (VPBs) and complex ventricular ectopy after immobilization and prevented stress-induced prolongation of the QT interval of VPBs throughout the 10-h experimental period. It also prevented prolongation of the QRS complex and fluctuations in the QT interval in normal sinus rhythm beats preceding VPBs during both immobilization and in the poststress period. Fast Fourier transform-based spectral analysis of heart-rate variability further showed that chewing significantly inhibited the stress-induced increase in the power ratio of low-to-high frequency activity (LF/HF: a marker of sympathetic activity) during immobilization and in addition was associated with blunting of the stress-induced increase in plasma noradrenaline observed at the termination of immobilization. Similar suppressive effects on the occurrence of VPBs and the LF/HF were observed in rats that were administered the β-adrenergic blocker propranolol before immobilization. These results indicate that chewing can ameliorate sympathetic hyperactivity during stress and prevent poststress arrhythmias and suggest that chewing may provide a nonpharmacological and cost-effective treatment option for patients with a high risk of stress-induced fatal arrhythmia.

sympathetic system and a hypoactive parasympathetic system (57). Stress-induced autonomic imbalance increases the occurrence of ventricular premature beats (VPBs), a possible indicator of susceptibility to sudden death (15, 30, 34, 49, 50), and interventions that control stress and reduce the occurrence of VPBs may reduce the propensity to cardiac sudden death (5). Pharmacological approaches to controlling stress-increased sympathetic responses and reducing ventricular arrhythmias have included administration of β-adrenergic blockers (45). However, sustained pharmacological therapy aimed at reducing VPBs in ambulatory patients is often accompanied by side effects (44). Alternative noninvasive and nonpharmacological approaches such as relaxation therapy and biofeedback may also reduce the occurrence of stress-induced VPBs (4, 9, 63).

We have previously demonstrated that chewing may represent an additional strategy for coping with stress both in humans and rodents. Chewing has been shown to suppress endocrine stress responses in the hypothalamic-pituitary-adrenal (HPA) axis (18, 36, 38). The hypothalamus plays an important role in central cardiovascular control (13), and the demonstration of a negative correlation between chewing and activation of the HPA axis suggests that masticatory stimulation could ameliorate stress-induced cardiac autonomic imbalance and reduce susceptibility to stress-induced arrhythmias by inhibiting neuronal responses in the hypothalamus. As a test of this hypothesis, we analyzed radiotelemetered electrocardiograms (ECGs) and plasma catecholamines in rats to determine whether chewing inhibits stress-induced autonomic imbalance and VPBs.

MATERIALS AND METHODS

Animals and stress protocol. We used 10-wk-old male Sprague-Dawley rats in these experiments. Animals were studied to ensure uniformity among experimental subjects and to minimize variations due to age, gender, and other factors such as diet habits that might affect cardiac function (8). We used only male rats to eliminate the effect of gonadal hormones on heart rate variability (HRV) variables (21, 43). Animals were individually housed in plexiglass cages measuring 40 × 25 × 15 cm and were kept in a room with controlled temperature (22 ± 3°C) and lighting (lights on from 8:00 AM to 8:00 PM). The bedding of the cages consisted of wood shavings. Food and water were freely available. This study was approved by the Animal Care and Use Committee of Kanagawa Dental College and conformed to the Guidelines for Care and Use of Laboratory Animals of the National Institutes of Health and the American Physiological Society. Efforts were made to minimize the number of animals used and their suffering.
We randomly divided rats into four groups (Fig. 1). Rats in the control group were not stressed (control group; CT). Rats in the stressed group were subjected to immobilization stress (stressed group; ST). To immobilize them, we fastened their limbs to a wooden board for 1 h in a spread-eagle, supine position. Rats in the stressed group with chewing were allowed to chew while subjected to immobilization stress (stressed with chewing group; SC). To characterize the effect of chewing, a wooden stick (diameter, 5 mm) was placed within reach of the rats during immobilization as described previously (37). Every rat in the SC group responded to the wooden stick by chewing on it with a rapid and repetitive sequence of jaw opening and closing movements for at least two-thirds of the total immobilization period. Rats in the propranolol treatment group were administered the β-adrenoceptor antagonist propranolol intraperitoneally (5 mg/kg; Sigma, Tokyo, Japan) immediately before immobilization stress (stressed with propranolol pretreatment group; ProST). Rats were returned to their home cages after immobilization, and ECGs continued to be recorded for the following 9 h. Plasma catecholamines were measured in a separate group of animals that were divided into two subgroups that were subjected to immobilization stress with or without chewing. Immobilization stress was induced between 9:00 AM and 10:00 AM in all experiments. Since all experimental procedures were conducted during the light phase, little or no spontaneous chewing behavior was observed in the animals (25) except in group SC during the experimental protocol, and our observations also suggested that rats had little food consumption in the postperiod.

ECG changes in response to immobilization stress. We made continuous radiotelemetric ECG recordings before, during, and after the period of immobilization stress. ECG transmitters measuring 31 × 16 × 10 mm (TA11CTA-F40; Data Sciences International, MN) were implanted subcutaneously in the abdominal cavity 2 wk before the experimental period. A wire loop positive electrode was fixed to the left of the xiphoid space caudal to the rib cage, and a negative electrode was fixed subcutaneously in the area of the right shoulder. This arrangement approximated an Einthoven Lead II configuration.

We investigated whether chewing alters sympathetic and parasympathetic activity under stress by evaluating HRV characterized and validated studies conducted in untethered rats (27, 39). We used HF and the ratio LF/HF as markers of parasympathetic and sympathetic activity, respectively (27).

VPBs were identified by visually inspecting individual ECG tracings, and the total number of events was counted and averaged within groups. VPBs were characterized by the following: 1) absence of P waves preceding a QRS complex; 2) large amplitude T waves with opposite polarity to the QRS complex; and 3) QRS interval of >20 ms. In quantifying total VPBs, each of the complexes occurring in clusters as couplets, triplets, or runs of ventricular tachycardia (VT) was counted individually and contributed to the total VPB count (Fig. 2). To further investigate ventricular ectopic activity in the SC and ST groups, we measured ECG parameters of the VPB and the three normal sinus rhythm (NSR) beats preceding it. Only ECG waveforms with detectable P, Q, R, S, and T waves were selected for this analysis, resulting in the exclusion of two rats each from the ST

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Fig. 1. Schematic representation of the protocol of the experiment. Rats were randomly assigned to one of four groups, a control group (CT), stressed group (ST), stressed with chewing group (SC), or stressed with propranolol pretreatment group (ProST). Following a 1-h TASK period, rats were returned to their home cages. ECGs were continuously recorded from 20 min before (PRE period) to 9 h after (POST period) the TASK period.

![Telemetered ECGs with examples of different arrhythmic events](http://ajpheart.physiology.org/)
and SC groups, ECG data in the CT and ProST groups were not subjected to this analysis due to an insufficient number of VPBs for statistical comparison. We measured the QRS complex, QT interval, and RQ’ interval of VPBs, and the PQ interval, QRS complex, and QT interval for NSR beats. The RQ’ interval is defined as the interval between the R wave of the preceding NSR beat and the Q wave of the following arrhythmia.

**Plasma catecholamine levels in response to immobilization stress.**

Plasma catecholamine levels were measured in an additional group of 18 rats to evaluate the degree of activation of the sympathetic nervous system by immobilization stress. These rats were divided into two subgroups that were treated in an identical fashion to the ST and SC groups. Blood was drawn from the caudal vein immediately before and after immobilization stress. At 1 h after immobilization stress, insufficient blood samples were obtained to permit HPLC determinations in 6 of the 18 rats and consequently only 12 rats were studied. The concentrations of plasma adrenaline, noradrenaline, and dopamine were determined by HPLC. All blood samples were immediately centrifuged (900 g) at 4°C for 25 min, and plasma was stored at −80°C until assayed. Each sample was mixed with dihydroxybenzylamine (1 ng/μl), alumina (300 μg/μl), and Tris HCl buffer (1.5 M, pH 8.6) containing 0.1 M Na2-EDTA (10 μl/μl). The mixture was then shaken for 10 min and centrifuged (1,000 g for 1 min) to sediment alumina. We washed the alumina three times with ultra-pure water, aspirating the supernatant each time. The alumina was transferred to the appropriate 0.22-μm filter tubes (Ultrafree-MC; Millipore). We added acetic acid (2%) containing 100 μM Na2-EDTA and allowed it to liberate adsorbed catecholamines for 5 min. Finally, the liberated catecholamines were obtained by centrifugation (2,000 g for 5 min).

The HPLC system was designed for analyzing trace biological samples (HETC-500; Eicom). Separation and detection were achieved in a phosphoric acid buffer (pH 5.7) containing sodium 1-octanesulfonate (600 mg/l), EDTA (50 mg/l), and Tris·HCl buffer (1.5 M, pH 8.6) containing 0.1 M Na2-EDTA (10 μl/μl). The mixture was then shaken for 10 min and centrifuged (1,000 g for 1 min) to sediment alumina. We washed the alumina three times with ultra-pure water, aspirating the supernatant each time. The alumina was transferred to the appropriate 0.22-μm filter tubes (Ultrafree-MC; Millipore). We added acetic acid (2%) containing 100 μM Na2-EDTA and allowed it to liberate adsorbed catecholamines for 5 min. Finally, the liberated catecholamines were obtained by centrifugation (2,000 g for 5 min).

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**Statistical analysis.**

We divided each ECG recording into three sections designated as PRE, TASK, and POST, which were defined as the 20-min period preceding stress exposure, the 1-h period of stress, and the 9-h period immediately following stress exposure, respectively. We counted the number of VPBs in TASK and POST. To quantify R-R interval parameters (HR and HRV), we further divided the POST period into nine 60-min subperiods (POST60, POST120, POST180, POST240, POST300, POST360, POST420, POST480, and POST540). Parameters were quantified as the mean for each period, including PRE, TASK, and all nine subperiods of POST. We compared the mean plasma catecholamine concentrations of both groups at each time point. Results were expressed as means ± SE. Unless otherwise stated, we compared the groups using one- or two-way ANOVA with repeated measures and the post hoc Tukey’s multiple comparison with Bonferroni correction.

**RESULTS**

**Effect of chewing on stress-induced VPBs.**

In the ST group immobilization stress caused a significant increase in total VPBs, and there were also occurrences of complex ventricular ectopy including bigeminy, couplets, triplets, and VT, both during the TASK and POST periods (Table 1). A representative example is shown in Fig. 2. As also shown in Table 1, the number of VPBs during the TASK period was comparable in the ST and SC groups, and both were significantly greater when compared with the CT group. The relatively large mean and variance values for VPBs in the SC group during the TASK period were caused by two outliers that had >40 VPBs during that period. On the other hand, there were significantly fewer VPBs in the SC than in the ST group during the POST period. Notably, there was also no complex ventricular ectopy (couplets, triplets, or VT) during the POST period in the SC group, in contrast to the presence of ventricular ectopy in the ST group. We also found that pretreatment with propranolol significantly suppressed the occurrence of VPBs both during the TASK and POST periods, and there were no significant differences in the number of VPBs comparing the SC, ProST, and CT groups during the POST period. These data indicate that both chewing and propranolol can reduce not only the number of poststress VPBs but also the presence of complex ventricular ectopy.

Analyzing ECG parameters of the VPBs and NSR beats that preceded VPBs in the ST group revealed that the QT interval of the VPBs was significantly longer than in the SC group both during the TASK and POST periods (Table 2). In addition, the QRS interval of NSR beats preceding VPBs was significantly longer in the ST than in the SC group during the TASK period (Table 3). It was also noted in the ST group during the POST period that the QT intervals of the second and third NSR beats...
preceding VPBs were significantly longer than for NSR beats immediately preceding VPBs, but this was not observed in the SC group (Table 3). Prolongation of the QRS complex and QT intervals indicates the presence of conduction delay and amplified electrical heterogeneities in the ventricles, respectively, providing a substrate for the development of life-threatening arrhythmias such as reentrant VT and torsade de pointes (3, 19). Abrupt shortening of the QT interval also increases susceptibility to the generation of VPB (12), possibly due to accelerated recovery of the myocardial refractory period. Our data suggest that chewing inhibits stress-induced prolongation of the QRS complex as well as fluctuations in QT intervals and by this mechanism suppresses the development of severe arrhythmias.

Effect of chewing on LF/HF ratios. As shown in Fig. 3A, immobilization stress significantly increased HR during TASK in both the ST (488 ± 9 beats/min) and SC (495 ± 14 beats/min) groups compared with the CT (353 ± 12 beats/min) group ($P < 0.05$). HR returned to the basal level 7 h after rats were released from stress. However, immobilization stress did not raise HR in the ProST group (371 ± 14 beats/min; Fig. 3A).

| TABLE 2. ECG parameters of VPBs during TASK and POST periods |
|-----------------|-----------------|-----------------|
|                 | QRS             | QT              | RQ'             |
| TASK            |                 |                 |                 |
| ST ($n = 7$)    | 31.1 ± 2.3      | 90.7 ± 3.2†     | 70.0 ± 2.2      |
| SC ($n = 8$)    | 28.6 ± 1.1      | 76.0 ± 2.5      | 72.3 ± 3.9      |
| POST            |                 |                 |                 |
| ST ($n = 12$)   | 26.6 ± 1.0      | 85.0 ± 2.6*     | 89.6 ± 8.4      |
| SC ($n = 8$)    | 26.4 ± 2.0      | 72.7 ± 4.0      | 86.2 ± 11.7     |

Mean values (±SE) for QRS complex, QT interval, and RQ' interval of each subject were measured (in ms) and averaged within each group. *$P < 0.05$, †significant difference compared with SC (Student’s $t$-test).

Immobilization stress significantly increased the LF/HF ratio in the ST group when compared with the CT group (0.57 ± 0.02 vs. 0.45 ± 0.02, respectively; $P < 0.05$), which lasted until 3 h after the end of TASK (Fig. 3B). However, chewing and pretreatment with propranolol inhibited the stress-induced rise in the LF/HF ratio compared with the ST group during immobilization (SC group 0.48 ± 0.03 and ProST group 0.42 ± 0.03; both $P < 0.05$, compared with the ST group), and the LF/HF ratio in the SC group was comparable to that in the CT and ProST groups for the entire measurement period including the period of immobilization (Fig. 3B). A significant increase in the LF/HF ratio was observed in the ProST group at the POST60 period (Fig. 3B), after which there was a trend toward
a gradual increase in HR (Fig. 3A). These results may be due to initial suppression of cardiac sympathetic activity followed by a rebound resulting from the rapid clearance of propranolol (46). On the other hand, HF was equally suppressed in the ST, SC, and ProST groups from the start of immobilization and returned to control levels 5 h after immobilization stress (Fig. 3C).

**Effect of chewing on catecholamine concentrations.** In agreement with earlier findings (41), immobilization stress significantly increased the response of all catecholamines including adrenaline, noradrenaline, and dopamine in the subgroup of 10 rats that were stressed without chewing (Fig. 4, A–C). Immobilization stress also significantly increased the plasma concentration of adrenaline and dopamine in the subgroup of eight rats that were stressed with chewing (Fig. 4, A and C), whereas the plasma concentration of noradrenaline was not significantly increased in this subgroup (Fig. 4B). The results indicate that chewing suppressed the release of noradrenaline resulting from immobilization stress but not adrenaline and dopamine. However, at 1 h after immobilization plasma catecholamine concentrations did not differ significantly from prestress levels, and there were also no differences between groups.

**DISCUSSION**

The key finding of the present study is that chewing not only reduced the overall occurrence of poststress VPBs but also completely abolished poststress complex ventricular ectopy. Based on the measurements of HRV and plasma catecholamine levels, the most likely underlying mechanism is suppression of the sympathetic response to immobilization stress. In the SC group, chewing also significantly suppressed prolongation of the QT interval and the QRS complex as well as fluctuations of the QT interval (Tables 2 and 3), indicating that chewing alters VPB characteristics. As noted earlier, there is a considerable body of literature indicating that stress-induced autonomic imbalance can facilitate ventricular arrhythmias and predispose to sudden cardiac death, particularly in patients with CVD (15, 30, 34, 49, 50). Although β-adrenergic blockers are widely used to prevent the occurrence of lethal arrhythmias that can result in sudden death, it seems desirable to develop a nonpharmacological therapy to control stress-induced sympathetic responses. To our knowledge this is the first study to demonstrate that chewing has an ameliorating effect on stress-induced arrhythmias.

Recent clinical investigations have demonstrated that gum chewing reduces postoperative ileus after gastrointestinal surgery (22, 26) and cesarean section (1, 23). Since sympathetic hyperactivity is one of the factors that promotes postoperative ileus (33), chewing may contribute to maintaining visceral autonomic balance and gastrointestinal homeostasis. Accordingly, the present study suggests that chewing gum may provide a nonpharmacological and inexpensive treatment option for patients with CVD.

Our experiment confirms previous research showing that severe stress triggers ventricular arrhythmias (28) by promoting autonomic imbalance between sympathetic hyperactivity and parasympathetic hypoactivity. Interestingly, our results in SC and ProST group rats indicate that selective suppression of sympathetic hyperactivity is sufficient to reduce poststress arrhythmias, even in the absence of differences in stress-attenuated parasympathetic activity in the three stressed groups. These results support earlier findings that sympathetic hyperactivity specifically favors the onset of cardiac arrhythmias (reviewed in Ref. 35). Although there remains some ambiguity about utilizing the LF component or the LF/HF ratio of HRV as pure markers of sympathetic modulation (56), our HRV analyses and plasma noradrenaline level measurements clearly indicate that chewing during immobilization alters cardiac autonomic responses and that these are associated with ventricular arrhythmia suppression in the poststress period.

Understanding the mechanism of the effect of chewing on reducing sympathetic activity is an important question. Some information on this point may be derived from our previous study (38) demonstrating that chewing interferes with stress-induced activation of the hypothalamus, one of several possible higher centers of cardiovascular regulation (16, 29, 53). Evidence suggests that stress triggers the release of corticotropin-

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Fig. 4. Plasma catecholamine levels [adrenaline (A), noradrenaline (B), and dopamine (C)] immediately before (PRE), immediately after (TASK), and 1 h after immobilization stress (POST60) in the 18 rats in the stressed without chewing subgroup (n = 10: filled columns) and stressed with chewing subgroup (n = 8; open columns). There were 6 rats in each subgroup at POST60. *Significant difference between PRE and TASK within each group; †significant difference between ST and SC in the TASK period (P < 0.05, multiple comparison after one-way ANOVA).
releasing factor in the paraventricular nucleus of the hypothalamus, which in turn may activate presympathetic neurons (48, 60, 61). Chewing is likely to suppress corticotropin-releasing factor release in the paraventricular nucleus of the hypothalamus (18) and attenuate sympathetic responses to stress by directly stimulating the trigemino-hypothalamic tract (31) or indirectly by inhibiting stress responses in the amygdala (55), which sends effferent fibers to the hypothalamus.

It may be noted that chewing failed to suppress arrhythmias during stress exposure, despite the significant suppression of sympathetic hyperactivity during that time period. Since chewing per se is a physical activity that may increase HR (51) and sympathetic activity (47), one possibility is that chewing during stress actually acted to facilitate arrhythmias (10). However, exercise-induced VPBs during physical activity are of little prognostic significance in healthy subjects (7), and in patients with a history of CVD the occurrence of frequent ventricular arrhythmias during recovery after exercise is a better predictor of an increased risk of death than arrhythmias occurring only during exercise (14). Indeed, the majority of VPBs that occurred during immobilization in rats in the SC group were single VPBs, which in patients with CVD might represent a lesser risk (30).

The underlying mechanism by which inhibition of sympathetic hyperactivity during stress exposure resulted in the suppression of poststress arrhythmia needs to be further elucidated. One hypothesis is that chewing prevented the stress-triggered alteration of the electrophysiological properties of the myocardium. Using isolated neonatal rat cardiac myocytes, Zhang et al. (62) showed that adrenergic stimulation for hours downregulated Kv4.3 mRNA and protein, a mediator of the transient outward potassium current (Ito). Attenuation of Ito increases the duration of the action potential and enhances repolarization heterogeneity, which is potentially arrhythmogenic. These previous findings suggest the possibility that the stressed rats in the current investigation, which showed sustained elevation of the sympathetic nervous activity for 4 h (Fig. 3B), may have developed adaptive redistribution of myocardial ion channels. Although we did not directly measure the electrophysiological properties of the myocardium of the rats, the prolonged and unstable QT intervals (Tables 2 and 3) in the poststress period of the stressed rats may reflect the effect of ion channel redistribution in causing action potential inhomogeneity. Since more prolonged stimulation of adrenergic receptors causes greater reduction in Kv4.3 mRNA (62), the cumulative duration of sympathetic hyperactivity could well determine the frequency of poststress arrhythmia.

Although much of the evidence from this study indicates that chewing suppresses an excessive sympathetic response to immobilization stress as judged by attenuation of the LF/HF ratio and lower adrenaline levels, it must be acknowledged that chewing did not suppress the increase in HR during immobilization stress. This discrepancy between HR and LF/HF ratio is mainly due to differences in LF, since values of HF for the ST and SC groups during TASK were similar. Acute increases in HR during stress are known to be due mainly to withdrawal of parasympathetic tone (42, 58). Furthermore, a number of previous studies have demonstrated that HR and the LF/HF ratio do not always change in parallel (24, 32, 43). In our study, the differing responses of HR and LF/HF ratio in the SC group could well be due to selective inhibition of sympathetic activity by chewing. Another potential discrepancy between HR and HRV parameters was observed in comparing results in the SC and ProST groups. HR in the ProST group rats remained at prestress levels while in SC group rats HR increased significantly during immobilization, despite the fact that the two groups showed comparable values for LF/HF ratio and HF. These results suggest that chewing, which has a behavioral aspect, and propranolol, which has pharmacological effects, regulate the HR response to stress differently, although they have comparable effects in preventing poststress VPBs. These differences may also relate to the effects of propranolol in the central nervous system. In addition to its actions on the heart, systemically administered propranolol may inhibit adrenergic responses in the amygdala (6, 20) to suppress HR increases, as has been noted in a study of water immersion stress (54).

In conclusion, chewing during stress exposure ameliorates sympathetic hyperactivity and stress-induced arrhythmias. Studies in humans further support the close relationship between masticatory function and cardiac autonomic function. Tooth loss has been associated with a higher risk of CVD (2), and malocclusion has been associated with a reduced HF component of HRV and a higher HR (11). Since chewing is a common behavior for both animals and humans, these results suggest that chewing may represent a useful way to reduce the risk of stress-induced ventricular ectopy in CVD patients. Human studies of chewing using similar end points may prove to be a worthwhile approach to validating the hypothesis that mastication can suppress autonomic imbalance and reduce cardiac risks.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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