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Selective serotonin reuptake inhibitors increase sympathetic activity under heavy alcohol exposure in rat models

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ABSTRACT

Aims: Self-medication with alcohol while being treated with antidepressants is a common problem in patients with depression. Both alcohol consumption and antidepressant administration can induce changes in the cardiac autonomic responses as indicated by heart rate variability (HRV). In this study, we examined cardiac autonomic responses induced by acute heavy alcohol exposure after SSRIs (selective serotonin reuptake inhibitors) medications.
Main methods: Rats were randomly divided into 3 groups, the alcohol administrated (Alc group), paroxetine administrated (SSRI group), and the SSRI + Alc group. Serum samples were collected to measure blood alcohol concentration (BAC). Physiological and cardiac autonomic responses including mean arterial pressure (MAP), heart rate (HR), and HRV were also compared among groups.
Key findings: The SSRI group exhibited higher values of HRV and HF (high frequency) than did the Alc and SSRI + Alc groups after alcohol administration. In contrast to the Alc group, the SSRI + Alc group had significantly lower MAP than Alc group, and higher HR, standard deviation of NN-intervals (SDNN), SDNN to MRR ratio (CVNN), square root of the mean squared differences of the successive NN-intervals (RMSSD) and HF values after alcohol administration.
Significance: Our results indicate that SSRIs increased sympathetic activity and alcohol reduced it in rats. The present study represents an attractive area for further research.

1. Introduction

Binge drinking can lead to an increase in blood alcohol concentration (BAC). Severe intoxication (300–500 mg/dL) is associated with deterioration of perception and serious physical reactions [9]. The repression of central nervous system (CNS) may result in stupor, hypotension, cardiac arrest and death [1,16]. Clinical manifestations of ethanol toxicity are often confounded by co-drug ingestions. A typical co-drug ingestion of acute alcohol intoxication is antidepressants [3].

The relationship between alcohol dependence and depressive disorders is of considerable theoretical significance. The alcohol ingestion may be an attempt at self-medication of depressive symptoms [2]. It is common that patients with depression self-medication with alcohol while being treated with antidepressants [13]. The serotonin reuptake inhibitors (SSRIs) are the widely prescribed antidepressant. SSRIs selectively block monoamine uptake sites with high affinity to serotonin uptake sites [5]. Paroxetine is the most potent serotonin reuptake blocker clinically available. Serotonin (5HT) has a coexistent link between alcohol and paroxetine [11,12]. Even single acute alcohol exposure altered various aspects of serotonin's synaptic functions [14]. Alterations in the dynamics of brain 5HT biosynthesis can lead to changes in cardiovascular function through the modulation of efferent sympathetic activity [8].

Responses to cardiac autonomic modulation include excitation and inhibition of sympathetic and vagal nervous activities. Heart rate and rhythm are largely under the control of the autonomic nervous system. Heart rate variability (HRV) is the amount of fluctuations from the mean heart rate [23]. HRV also represents one of the most promising markers, which are signs of increased or reduced sympathetic and vagal activity. Efferent vagal activity is a major contributor to the high-frequency range (HF, from 0.15 to 0.4 Hz) component. However, the interpretation of the low-frequency range (LF, from 0.04 to 0.15 Hz) component is more controversial. HRV is one of parameters that include both sympathetic and vagal influences [22,24]. It is critical to recall that during sympathetic activation, the resulting tachycardia is typically accompanied by a marked reduction in total power, whereas the reverse occurs during vagal activation. The changes in total power influence LF and HF in the same direction and prevent the appreciation of the fractional distribution of energy [7].

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Serotonin may underlie the link between HRV and depression, and low HRV may be related to mood and poor affective processing through changes in serotonin function [8]. In addition, a report on paroxetineinduced increase of heart rate variability indicated potential benefits of SSRI in decreasing cardiac mortality in panic disorders [25]. Many studies have discussed on the relationship between alcohol consumption and heart disease [19]. In addition, acute alcohol consumption resulted in increasing HRV consistent with autonomic parasympathetic activation [27]. A significant inverse correlation was observed between HRV and both the severity of depression and the duration of the depressive episode [17]. To date, HRV change induced by SSRIs combined with alcohol has not been fully investigated. In this study, we used a rat model to simulate and examine the consequence of SSRIs combined with acute alcohol administration on cardiac autonomic activity.

2. Materials and methods

2.1. Experimental design

This study was an experimental result subsequent to our previous study which had already been completed in 2013 [6]. Thirty-six male Wistar rats, weighing 290–310 g, were housed 2 per cage and kept on a 12:12 h reversed light/dark cycle (lights on at 7 A.M.) in a temperature-controlled room (22 ± 1 °C).The rats were randomly divided into 3 groups ($n = 12$ for each group),the alcohol administrated (Alc) group, paroxetine administrated (SSRI) group, and SSRI + Alc administrated group. Femoralarterial and vein cannulations were performed before drug administration. The rats were anesthetized using inhalation for approximately 15 min. A polyethylene catheter (PE-50) was inserted into the right femoral artery to collect blood samples and was connected to a pressure transducer (Gould Instruments, Cleveland, OH, USA) to record blood pressure and heart rate on a polygraph recorder (Power Lab; AD Instruments, Mountain View, CA, USA). All procedures were performed under sterile conditions and were the same as described in previous study [10]. After the operation, animals were placed in a metabolic cage.

2.2. Alcohol and SSRI administration

The administration of drug was begun at 8 h after operation. In this experiment, rats were kept in conscious status. The 95% edible alcohol (Taiwan Sagur Co., Taiwan)was diluted with distilled water to reach 40% volume/volume concentration. The Alc group and SSRI + Alc group received ethanol at 5 g/kg of body weight, administered over 3 h through slow intravenous infusion, using an infusion pump. The amount of 40% ethanol was really infused in the range from 4.52 to 4.85 ml/3 h (for BW from 290 g to 310 g) in this study. The ethanol dosage of 5 g/kg was selected [21] to generate a blood alcohol concentration of over 300 mg/dL without causing death, as determined in our previous study [6]. The SSRI and SSRI + Alc groups were administered paroxetine (0.33 mg/kg of body weight) through a feeding tube before receiving distilled water and ethanol infusions. The dosage of paroxetine (Standard Chem. & Pharm. Co., Taiwan) was selected according to the daily starting dose (20 mg/d) administrated and the minimal effective dose applied to a normal 60-kg human adult. For most patients, 20 mg/d will also be the optimal dose [4]. The protocols used were approved by the Institutional Animal Care and Use Committee of Tzu Chi University (No. 98070) and were consistent with the standards for the care and use of laboratory animals as outlined in the NIH Guide.

2.3. Blood samples, blood pressure, and heart rate collection

Blood samples were taken from the femoral arterial catheter before alcohol or saline infusion (marked as pre in the figures), and at 0 (the time point at infusion finished), 1, 3, 6, 9, 12, 18, and 24 h after the alcohol or saline infusion. Blood alcohol concentrations were measured immediately after blood was withdrawn. The data of the arterial blood pressure (MAP) and HR were also collected at pre, 0, 1, 3, 6, 9, 12, 18, and 24 h.

2.4. HRV analysis

Tools for measurement of cardiovascular responses include the software package of ECG data recording (PowerLab, AD Instruments, Mountain View, CA, USA), LabChart's HRV add-on and the other custom-design software for data processing. Based on ECG data recorded from rats, the software performs robust beat detection and power spectral analyze. HRV is the physiological phenomenon of variation in the time intervals between heartbeats. The interval between adjacent QRS complexes is referred to as the normal to normal (NN) or the R to R (RR) intervals, and HRV is defined as the variation of the RR intervals [24]. Two major approaches for short-term HRV analysis exist, namely time-domain and frequency-domain analysis. Five-minute ECG recordings were used for the time-domain analysis. The most stable continuous time segment was selected for the time-domain analysis. The mean of all the RR intervals (MRR), standard deviation of all NN-intervals (SDNN or HRV), SDNN to MRR ratio (CVNN or %HRV) and square root of the mean squared differences of the successive NN-intervals (RMSSD or dHRV) were calculated from the data.

2.5. Autonomic regulation of activity power

For frequency-domain analysis, the RR interval sequences were resampled using a fast Fourier transform-based method to equal intervals. Because the rat and human heart rates differ, we reselected the frequency ranges in the animal model of rats for this study. Two frequency bands were determined, namely LFas 0.2–0.8 Hz and HF as 0.8–2.5 Hz [18]. Power was estimated as the area under the spectrum within these frequency ranges. The indices included LF power, HF power, and LF/HF ratio. The LF/HF ratio represented the sympatho-vagal balance of the autonomic nervous system (ANS). The normal range of the LF/HF ratio was 0.8 to 1.5, and −0.223 to 0.405 in the natural logarithm. We analyzed the SDNN and relative variation CVNN at pre, 0, 1, 3, 6, 9, and 12 h in percentage units to determine a long-term measure. This measure presented the comparative range of regulation excluding the variation of the RR intervals.

2.6. Statistical analysis

Data were expressed as mean ± SD, and analyses were conducted using the SPSS 13.0 software. For statistical differences between groups at each time points, data were subjected to one-way analysis of variance (ANOVA), using Duncan's post-hoc multiple comparisons. Statistical significance was set at $p < 0.05$ (2-tailed).

3. Results

3.1. Blood alcohol concentration and basic cardiac physiology

The mean values of the BAC in the Alc and SSRI + Alc groups were approximately 475 mg/dL at the end of the alcohol infusion (0 h) (Fig. 1A). The BAC of the SSRI group was significantly lower than that of the Alc and SSRI + Alc groups at 0, 1, 3, 6, 9, and 12 h ($p < 0.05$). Accordingly, the alcohol half-life of the Alc and SSRI + Alc groups were 6.9 and 7.8 h, respectively.

MAP and HR were measured for showing how drug effects on ANS. The mean MAP values after alcohol infusion differed significantly across the 3 groups at each time point. Compared with the SSRI group, hypotension occurred at 0, 1, 3, 6, 9, and 12 h in the Alc group and SSRI + Alc group (Fig. 1B), and were lower than those of the SSRI group ($p < 0.05$). The lower MAP was simultaneous with the higher BAC throughout the first hour until the 12th h in the alcohol experiments. However, the SSRI administrations enhanced the MAP decrease.