

# Suppression of Mental Stress-induced Changes by Tansospirone, an Anxiolytic, in Cardiovascular Function

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**Summary.** Effects of anxiolytics on mental stress-induced changes in heart rate and blood pressure were investigated in 54 healthy volunteers, 21-24 years of age, by double blind protocol. The mental stress induced by a computerized color word conflict test increased heart rate and systolic and diastolic blood pressure by  $4.2 \pm 1.0$  /min,  $5.2 \pm 1.9$  mmHg and  $5.9 \pm 1.9$  mmHg, respectively. Tansospirone citrate (*p.o.*, 5 mg), a 5HT<sub>1A</sub> receptor agonist, did not change the resting heart rate or resting blood pressure three h after administration, whereas metoprolol (*p.o.*, 20 mg), a  $\beta$ 1-adrenoceptor antagonist, gradually reduced the resting heart rate and resting systolic blood pressure. Tansospirone significantly inhibited the mental stress-induced increase in heart rate three h after administration, just as metoprolol did. These findings suggested that a low dose of tansospirone selectively prevents the mental stress-induced changes in cardiovascular activity without affecting the resting state.

**Key words**— anxiolytic, tansospirone, mental stress, color word conflict test, heart rate, blood pressure.

## INTRODUCTION

Mental stress often activates sympathetic nerve activity in ordinary life and increases blood pressure and heart rate in healthy and/or ill persons. In particular, cardiovascular diseases, such as hypertension, angina pectoris and tachyarrhythmia, are exacerbated by enhanced sympathetic nerve activity which results from mental stress. It is therefore desirable to lessen

mental stress with appropriate treatments, for example,  $\beta$ -adrenoceptor blockade.<sup>1-5)</sup>

To study the effect of  $\beta$ -adrenoceptor blockers ( $\beta$ -blockers), we established a mental stress model by a computerized color word conflict test in healthy volunteers.<sup>6)</sup> We then examined the protective effects of two different  $\beta$ -blockers, metoprolol and carvedilol, on the mental stress-induced changes in cardiovascular functions. Metoprolol, a  $\beta$ 1-selective blocker without specific vasodilating properties, reduced both systolic and diastolic blood pressure and heart rate through the selective inhibition of cardiac  $\beta$ 1-adrenoceptor, and inhibited mental stress-induced changes in cardiovascular functions.<sup>6,7,8,9)</sup> Carvedilol, which is another  $\beta$ -blocker with nonselective  $\beta$ -blockade<sup>10)</sup> and a weak  $\alpha$ 1-adrenoceptor blocking property,<sup>10,11,12)</sup> also inhibited mental stress-induced changes in cardiovascular functions. These findings using  $\beta$ -blockers support the idea that a  $\beta$ -adrenoceptor blockade inhibits mental stress-induced changes in cardiovascular functions. Besides the protection against the mental stress-induced changes, however,  $\beta$ -blockers — such as metoprolol and carvedilol, have an inhibitory action on the resting systolic and diastolic blood pressure and heart rate.<sup>5,6,13)</sup> This disadvantage might impede clinical use of these  $\beta$ -blockers against mental stress-induced changes in cardiovascular functions because of the possible dysfunction of the cardiovascular circulation arising from their influence on the resting state.

The serotonergic 5HT<sub>1A</sub> receptor is related to the regulation of emotions; its receptor agonists can induce anxiolytic effects in humans and animals.<sup>14,15,16)</sup> It was reported that 5HT<sub>1A</sub> receptor agonists may be effective in stress-induced behavioral symptoms of depression.

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**Abbreviations**— ANOVA, analysis of variance; 5-HIAA, 5-Hydroxyindole acetic acid, 5-HT, serotonin;  $\beta$ -blocker,  $\beta$ -adrenoceptor blocker.

The 5HT<sub>1A</sub> receptor partial agonist, tandospirone, is an azapirone derivative like buspirone and has anxiolytic effects.<sup>17-22)</sup> However, the effect of tandospirone on mental stress-induced changes in cardiovascular function in humans has not yet been clarified. We therefore investigated the effect of an anxiolytic, tandospirone, on mental stress-induced changes in heart rate and blood pressure in order to determine the specific drug which affects only mental stress-induced changes but not the resting cardiovascular functions.

## MATERIALS AND METHODS

### Volunteers

Fifty-four healthy Japanese volunteers, 21-24 years of age (46 men and eight women), participated in this study. Individuals who had a history of bronchial asthma, allergic disorder, and cardiovascular diseases were excluded. All agreed to the purpose of this study and offered informed consent according to the protocol by the review board of Niigata University Medical School.

### Drugs

Metoprolol tartrate was purchased from AstraZeneca Co. Ltd.. Tandospirone citrate was purchased from Sumitomo Pharmaceutical Co. Ltd.. A tablet of lactamine (Biofermin, Takeda Pharmaceutical Co. Ltd., Osaka) was taken up as a placebo.

### Protocol

The protocol of this double blind study was performed as described elsewhere.<sup>6)</sup> A computerized version of the Stroop's color word conflict test was taken as mental stress; this produced more profound stimulation on the sympathetic function than that on the Kleperin psychiatric arithmetic test.<sup>23)</sup> The color word conflict test was performed 200 times for four min. To increase the effect of the color word conflict test as a stressor, the interval of each trial was shortened to 1.2 sec. Before and immediately after each set of mental stress tests, heart rate and systolic and diastolic blood pressure were measured. Blood pressure was measured by manometer, and heart rate was calculated by counting the pulse for 30 sec and doubling the value obtained there. The first set of mental stress tests was performed before drugs were administered at 1:30 p.m. Then each drug or placebo was administered orally under the double blind protocol. The second and third sets of mental stress tests were performed one and three h after drug administration, respectively. There were no volunteers who experienced any trouble or sickness under this study protocol.

### Data analysis

Data are means  $\pm$  standard error. Student's *t*-test or ANOVA followed by a post-hoc analysis was employed to detect the effect of the  $\beta$ -blocker and tandospirone on the resting cardiac functions and mental stress-induced changes in cardiovascular functions.  $P < 0.05$  was considered to be significant.

## RESULTS

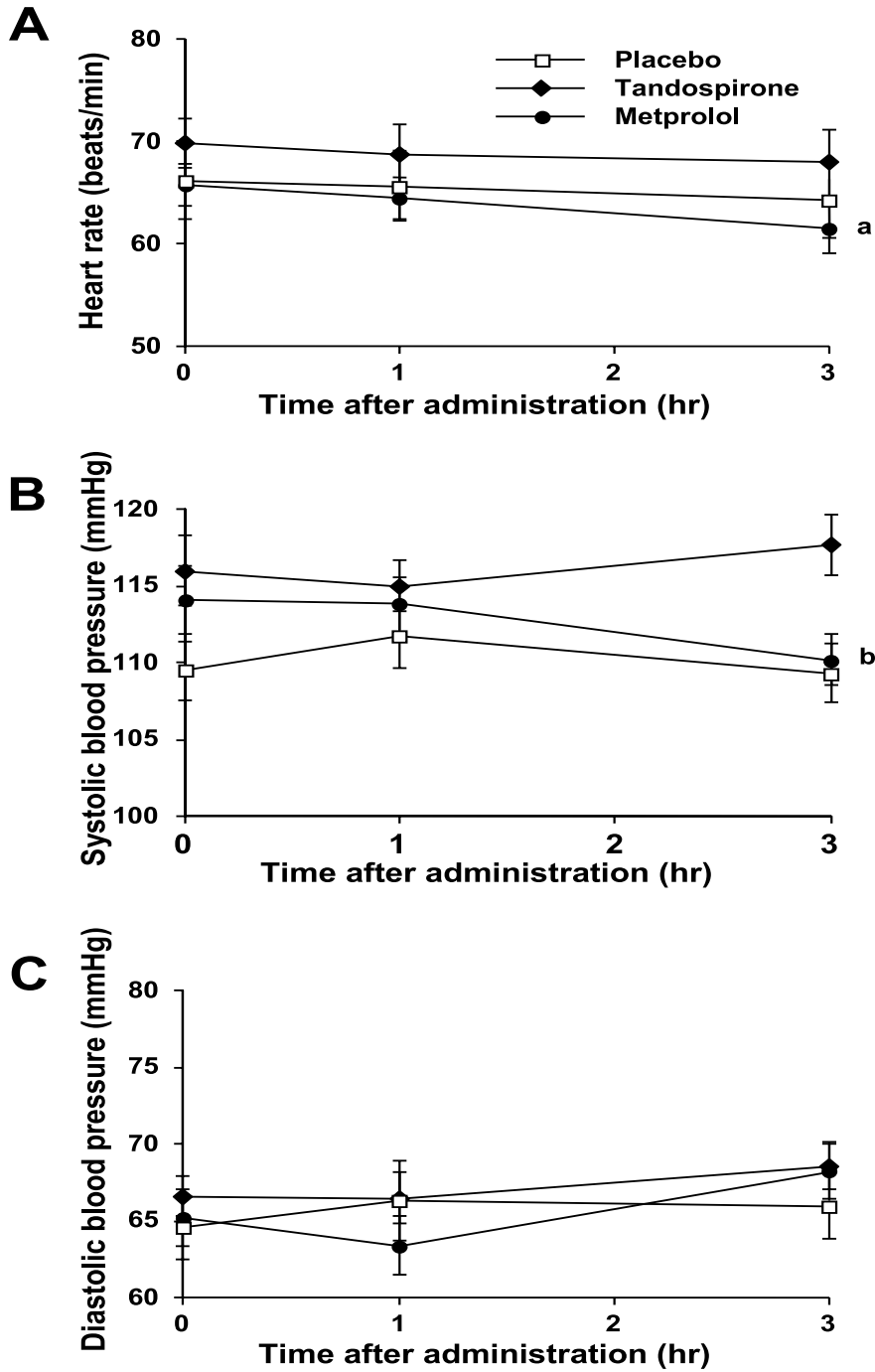
### Effect of tandospirone on resting heart rate and blood pressure

Fig.1 shows the effects of tandospirone and metoprolol on the resting heart rate and resting blood pressure. During the experimental period, the resting heart rate of subjects was constant in the placebo and tandospirone groups, but it gradually decreased in the metoprolol group, probably due to the  $\beta_1$ -blockade effect on the heart (Fig.1A). The decrease in heart rate by the  $\beta$ -blocker was modest but significant, as previously reported.<sup>6)</sup> The difference was not significant one h after oral administration, but rather after three h.

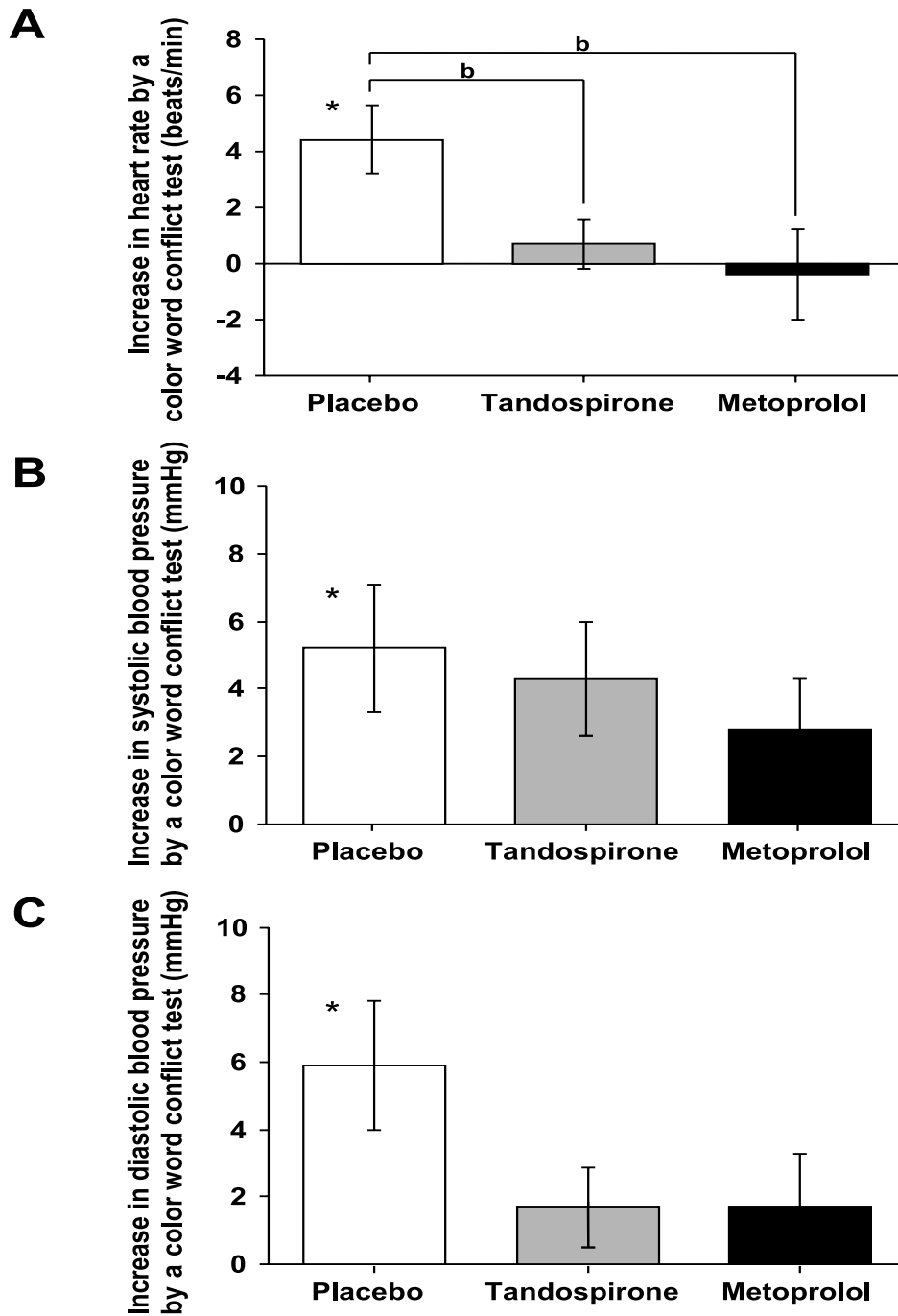
As shown in Fig.1B, the resting systolic blood pressures in the placebo and tandospirone groups were constant during experimental period. Metoprolol caused a slight, however, significant reduction of the systolic blood pressure three h after oral administration. This reduction was also probably due to the  $\beta_1$ -blockade effect on cardiac output, which was reported in the previous study.<sup>6)</sup> In contrast, the resting diastolic pressure did not change in any groups during the experimental period (Fig.1C). Treatment with 20 mg metoprolol or 5 mg tandospirone did not decrease the diastolic blood pressure. Thus a low dose of tandospirone (5 mg) did not affect the resting cardiovascular functions (heart rate and blood pressure), unlike the effect of  $\beta$ -blockers.

### Color word conflict test-induced increases in blood pressure and heart rate

Changes in heart rate and blood pressure induced by a computerized color word conflict test were measured as a consequence of mental stress, as shown in Fig.2. A color word conflict test increased the heart rate and systolic and diastolic blood pressure modestly but significantly in the placebo group (by  $4.2 \pm 1.0$  /min,  $5.2 \pm 1.9$  mmHg, and  $5.9 \pm 1.9$  mmHg, respectively) during the experimental period. The color word conflict test-induced changes in cardiovascular functions were the same before and one h and three h after an oral administration of the placebo, suggesting the absence of acclimation to the test under



**Fig. 1.** Effects of tansospirone and metoprolol on resting heart rate and blood pressure. Heart rate and systolic and diastolic blood pressure of healthy volunteers at rest were measured before, and one and three h after oral administration of agents. **A.** Effect on heart rate. **B.** Effect on systolic blood pressure (SBP). **C.** Effect on diastolic blood pressure (DBP). Each value indicates mean and S.E.M. of the placebo group (□; n =18), tansospirone group (◆; n =18), and metoprolol group (●; n =18). The two-way analysis of variance (ANOVA) was significant ( $F = 3.06, P = 0.01$ , no interaction between time and drugs) and the differences between 0 and three h after oral administration for the metoprolol group are indicated by Bonferoni’s post-hoc tests, a,  $P < 0.05$ ; b,  $P < 0.05$ . Paired *t*-test was also performed between 0 and three h after oral administration for the metoprolol group. a,  $P < 0.01$ ; b,  $P < 0.025$ .



**Fig.2.** Effects of tandospirone and metoprolol on a color word conflict test-induced increase in heart rate. Effects of tandospirone and metoprolol on a color word conflict test-induced increase in heart rate. **A.**, systolic **B.** and diastolic **C.** blood pressure were measured three h after oral administration. Each value indicates changes (mean  $\pm$  S.E.M.) induced by a color word conflict test on the placebo, tandospirone, and metoprolol groups ( $n = 18$  each). Student's *t*-test was performed and the data immediately after the color word conflict test were compared with the values before the test (\*,  $P < 0.05$ ). The one-way ANOVA analysis was significant ( $F = 3.18$ ,  $P = 0.03$  in the case of heart rate) and the data from the tandospirone and metoprolol groups were compared with the value of the placebo group by Dunnett's post-hoc test,  $b$ ,  $P < 0.05$ .

the present conditions (data not shown).

### Effects of an oral administration of tandospirone on mental stress-induced changes in heart rate

Metoprolol (20 mg) inhibited the mental stress-induced increase in heart rate three h after oral administration (Fig.2A), though not one h after administration (data not shown). Tandospirone (5 mg) also protected the mental stress-induced increase in heart rate under the present conditions, just as metoprolol did (Fig.2A). The mental stress-induced increase in systolic blood pressure was not significantly inhibited by treatment with tandospirone or metoprolol three h after oral administration (Fig.2B). As for the diastolic blood pressure, tandospirone and metoprolol tended to suppress the mental stress-induced increase, but not significantly. These findings indicated that a low dose of tandospirone selectively inhibited the increase in heart rate induced by a color word conflict test (mental stress), without influencing cardiovascular activity in the resting state.

## DISCUSSION

Mild mental stress such as computer-based events is very common in ordinary life nowadays. The present study indicated the protective effect of an anxiolytic, tandospirone, as well as a  $\beta$ -blocker, metoprolol, on mental stress (a computerized color word conflict test)-induced increases in heart rates.

It has been shown that  $\beta$ -blockers reduce the resting heart rate and the resting blood pressure and that they also suppress the increases in blood pressure and heart rates triggered by sympathetic nerve stimuli during mental stress.<sup>6,7,13,23,24</sup> In spite of their suppression of resting cardiovascular functions,  $\beta$ -blockers more profoundly inhibited mental stress-induced changes in heart rates and blood pressure by a computerized color word conflict test because they exerted action on mental stress-induced changes at much lower concentrations than the effective doses at rest or during exercise<sup>6,12,13</sup> (shown in Fig.1). Mental stress-induced changes in cardiovascular functions seem to be much dependent on the activation of cardiovascular  $\beta$ -adrenoceptors in the periphery. During mental stress, the increase in the plasma epinephrine level is higher than that in the norepinephrine level,<sup>9,24</sup> and the  $\beta_1$ -blocker, metoprolol, reduces the plasma epinephrine level.<sup>9</sup> Therefore the inhibition by metoprolol of mental stress-induced changes in the heart rate might result from the suppressed plasma epinephrine level.

In contrast to metoprolol, a low dose (5 mg) of tandospirone did not influence the resting blood pressure and heart rates, though it selectively reduced

the mental stress-induced increase in heart rates. This selectivity of tandospirone on the mental stress-induced changes in cardiovascular function seems to be due to its pharmacological action on the central serotonergic nervous system.<sup>15,17-20</sup> In humans as well as other animal species, 5HT<sub>1A</sub> receptors are distributed mainly in the brain regions concerned with mood and anxiety.<sup>15,16,17</sup> The 5HT<sub>1A</sub> receptors in the raphe neurons are predominantly somatodendritic autoreceptors.<sup>16</sup> Tandospirone exerts its agonistic action on these presynaptic 5HT<sub>1A</sub> receptors of the serotonergic neurons in the raphe nucleus, so that the activity of these neurons is decreased.<sup>17,18,19</sup> Eventually, the administration of tandospirone results in a decrease in the turnover rate of 5-Hydroxyindole acetic acid/serotonin (5-HIAA/5-HT) in the hypothalamus, hippocampus, and midbrain<sup>21</sup> and also in attenuation to stress by inhibiting serotonergic neuron firing in the limbic regions.<sup>15,19,21</sup> Thus, the selectivity of tandospirone on mental stress-induced changes in cardiovascular function presumably depended on its action on the central nervous system. Tandospirone appears to be a useful drug for managing mental stress because of its selectivity for mental stress-induced changes in cardiovascular function.

Further studies are required to elucidate the selective mechanism of tandospirone for stress induced by mental causes in humans.

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