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# Effect of combined treatment with noradrenaline and serotonin reuptake inhibitors on conditioned freezing

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**Abstract**

To clarify the therapeutic interaction between serotonin and noradrenaline reuptake inhibition on fear, this study examined the acute and subchronic effects of combined treatment with the selective serotonin reuptake inhibitor citalopram and the selective noradrenaline reuptake inhibitor reboxetine on the expression of conditioned fear (re-exposure to an environment paired previously with inescapable electric footshocks). After fear conditioning was achieved with footshocks, the drugs were administered to rats and freezing behavior, as an index of fear, was observed in the shock chamber. Acute and subchronic treatment with citalopram was reproducibly anxiolytic against conditioned freezing. Acute reboxetine worsened conditioned freezing and reversed the acute anxiolytic effects of citalopram, but this anxiogenic effect of noradrenaline reuptake inhibition was not observed after subchronic treatment. These results suggest that adding noradrenaline reuptake inhibitors to serotonin reuptake inhibitors adversely affects fear, at least with acute treatment.


*Keywords:* Conditioned fear; Selective serotonin reuptake inhibitor; Selective noradrenaline reuptake inhibitor; Noradrenaline; Serotonin; Anxiety disorder

## 1. Introduction

Since the 1960s, imipramine and clomipramine, tricyclic antidepressants that block serotonin reuptake, have been effective in treating various anxiety disorders, such as panic and obsessive–compulsive disorders, and have been widely used in clinical practice (Zohar and Westenberg, 2000). The clinical mean antipanic dosage of antidepressants for panic disorder is significantly correlated with the potency of these drugs in inhibiting serotonin reuptake (Erikkson and Humble, 1990). The clinical efficacy of selective serotonin reuptake inhibitors for most anxiety disorders has been established in several double-blind, placebo-controlled trials (Zohar and Westenberg, 2000). However, noradrenaline reuptake inhibition by imipramine and clomipramine appears not to be involved in the clinical efficacy of tricyclic antidepressants in anxiety disorders, because in a double-blind study the selective serotonin reuptake inhibitor fluvoxamine had a better effect than the noradrenaline reuptake inhibitor maprotiline in treating panic disorder (Den Boer and Westenberg, 1988). Nevertheless, the role of noradrenaline reuptake inhibition in the therapeutic effects of antidepressants for anxiety disorders has not been fully clarified, and whether the contribution of noradrenaline in the treatment of anxiety disorders is nil, negative, or positive is not clear.

Recently, the clinical efficacy of venlafaxine, a serotonin–noradrenaline reuptake inhibitor, in the treatment of generalized anxiety disorder and social anxiety disorder was investigated in double-blind, placebo-controlled studies (Allgulander et al., 2004; Meoni et al., 2004). Compared with the selective serotonin reuptake inhibitor paroxetine, venlafaxine showed a comparable efficacy and safety in treating social anxiety disorder (Allgulander et al., 2004). Thus, clinical studies provide no information on the advantage or disadvantage of serotonin–noradrenaline reuptake inhibitors compared with selective serotonin reuptake inhibitors, or on the pharmacological impact of noradrenergic activation on anxiety. However, preclinical evidence suggests that noradrenergic activation is involved in inducing anxiety and its inactivation may be related to the relief of anxiety in animals (Tanaka et al., 2000). This preclinical finding casts doubt on the therapeutic role of

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noradrenaline reuptake inhibition in the anxiolytic effects of serotonin–noradrenaline reuptake inhibitors and tricyclic antidepressants.

Although clinical trials are most valuable for clarifying the mechanisms underlying anxiolytic effects and provide well-judged theories, preclinical experiments are essential for determining the interaction between serotonin and noradrenaline reuptake inhibition in fear and anxiety. Traditional animal models of fear and anxiety have failed to show the anxiolytic effect of selective serotonin reuptake inhibitors (Borsini et al., 2002). Conditioned fear, a simple animal model of fear, has been thoroughly investigated by many neuroscientists, whose recent studies have shown the neuronal mechanism of fear (LeDoux, 2000). Conditioned fear stress is a sensitive model of fear for detecting the anxiolytic effect of selective serotonin reuptake inhibitors in animals (Hashimoto et al., 1996; Inoue et al., 1996), but noradrenaline reuptake inhibitors do not affect fear in this model (Hashimoto et al., 1996). In conditioned fear, the classic anxiolytic benzodiazepines and 5-$HT_{1A}$ receptor agonists also show anxiolytic effects (Inoue et al., 1996; Li et al., 2001).

To clarify the therapeutic interaction between serotonin and noradrenaline reuptake inhibition on fear, we examined the acute and subchronic effects of combined treatment with citalopram, a selective serotonin reuptake inhibitor (Brunello and Racagni, 1998), and reboxetine, a selective noradrenaline reuptake inhibitor (Brunello and Racagni, 1998), on contextual conditioned freezing behavior, an index of fear, caused by a contextual stimulus when rats were re-exposed to a shock chamber where they had previously received aversive footshocks. The purpose of this study was to verify the hypothesis that noradrenergic activation increases fear, whereas serotonergic activation decreases fear in an animal model. We also discuss the clinical implications of using a noradrenaline reuptake inhibitor in the treatment of fear.

## 2. Materials and methods

### 2.1. Animals

Male Sprague–Dawley rats from Shizuoka Laboratory Animal Center (Shizuoka, Japan), weighing 230–250 g during the conditioned fear test, were housed in groups of four and were maintained in a 12-h light:12-h dark (light phase; 06:30–18:30 h), temperature-controlled environment (22 ± 1 °C) with free access to food and water. Conditioning began after a 2-week period of acclimatization. Rats were tested between 8:00 h and 13:00 h. All procedures were approved by the Hokkaido University School of Medicine Animal Care and Use Committee, and complied with the Guide for the Care and Use of Laboratory Animals, Hokkaido University School of Medicine.

### 2.2. Drugs

Citalopram hydrobromide (H. Lundbeck A/S, Copenhagen, Denmark) and reboxetine methansulphonate (Pharmacia and Upjohn, Milano, Italy) were dissolved separately in 0.9% saline as 1 ml/kg and were injected subcutaneously (s.c.). Saline alone was administered as a control. The dose (10 mg/kg) of citalopram was chosen because it reduced conditioned freezing significantly in our previous study (Hashimoto et al., 1996). A high dose (10 mg/kg) of reboxetine was used to increase extracellular noradrenaline levels and to inhibit noradrenaline reuptake in vivo. A low dose (1 mg/kg) of reboxetine was less effective in increasing extracellular noradrenaline levels than 10 mg/kg of reboxetine (Riva et al., 1989; Kitaichi et al., 2004).

### 2.3. Apparatus and conditioning

For contextual fear conditioning, rats individually underwent inescapable electric footshocks for a total of 2.5 min in a shock chamber with a grid floor (19 × 22 × 20 cm, Medical Agent Co., Japan) (Hashimoto et al., 1996). Electric shocks were applied by using a Model SGS-02D Shock Generator (Medical Agent Co., Japan). Five footshocks (2.5-mA scrambled shock, each of 30 s duration) were delivered at intershock intervals of 35–85 s (mean 60 s).

### 2.4. Behavioral procedures

The rats that were contextually conditioned to the shock chamber were grouped 8–16 rats per group. In an acute experiment, drugs were given s.c. at 24 h after fear conditioning, and the rats were again placed in the shock chamber 4 h after the injection and were observed for 5 min without shocks. In a subchronic experiment, drugs were administered s.c. once a day for 7 days from 24 h after fear conditioning; the rats were again placed in the shock chamber 4 h after the final injection and were observed for 5 min without shocks. Conditioned fear, as measured by freezing, develops from the contextual stimuli of the conditioned chamber (Fanselow, 1980). The duration of freezing behavior was recorded by using a time-sampling procedure (Fanselow, 1980), modified as previously described (Hashimoto et al., 1996). Freezing was defined as the absence of all observable movement of the skeleton and the vibrissae, except movements related to respiration. The rat behavior was classified as either freezing or active during 10 s. The percentage score of freezing behavior represents the number of 10-s periods during which the rats froze for the entire 10 s.

In the experiment on the effect of reboxetine and citalopram on freezing in unshocked rats, rats were placed in the shock chamber without shocks for 5 min, and drugs were given s.c. 24 h later. The rats were again placed in the shock chamber 4 h after the injection and were observed for 5 min without shocks.

### 2.5. Data analysis

All data are means ± S.E.M. of the individual values of the rats from each group. Statistical analysis of the data was done by using two-way analysis of variance (ANOVA), followed by Duncan's test for multiple comparison as a post hoc test when interaction was significant. Statistical significance was set at $P < 0.05$.

## 3. Results

### 3.1. Acute effect of combined treatment with citalopram and low-dose reboxetine on conditioned freezing

Acute administration of citalopram at a dose of 10 mg/kg reduced conditioned freezing significantly [2-way ANOVA, effect of citalopram alone, $F(1, 60)=4.399$, $P=0.0402$]. Acute reboxetine at a dose of 1 mg/kg did not affect conditioned freezing [2-way ANOVA, effect of reboxetine alone, $F(1, 60)=2.775$, $P=0.101$]. The interaction between citalopram and reboxetine was not statistically significant [2-way ANOVA, interaction, $F(1, 60)=1.168$, $P=0.2841$] (Fig. 1).

### 3.2. Acute effect of combined treatment with citalopram and high-dose reboxetine on conditioned freezing

Acute administration of citalopram at a dose of 10 mg/kg reproducibly reduced conditioned freezing significantly [2-way ANOVA, effect of citalopram alone, $F(1, 28)=6.386$, $P=0.0174$]. However, acute reboxetine at a dose of 10 mg/kg increased conditioned freezing significantly [2-way ANOVA, effect of reboxetine alone, $F(1, 28)=7.506$, $P=0.0106$]. The interaction between citalopram and reboxetine was not statistically significant [2-way ANOVA, interaction, $F(1, 28)=0.758$, $P=0.3913$], indicating that acute high-dose reboxetine alone increases conditioned freezing and counteracts the reduction of conditioned fear induced by citalopram (Fig. 2).

### 3.3. Subchronic effect of combined treatment with citalopram and high-dose reboxetine on conditioned freezing

Subchronic administration of citalopram and high-dose reboxetine for 7 days revealed a significant interaction between citalopram and reboxetine, but the effects of citalopram or reboxetine alone were not significant [2-way ANOVA, effect of citalopram alone, $F(1, 60)=3.172$, $P=0.08$; effect of reboxetine alone, $F(1, 60)=0.099$, $P=0.7541$; interaction, $F(1, 60)=4.584$, $P=0.0363$]. The Duncan post hoc test showed a significant difference only between the saline group and the citalopram group (Fig. 3).

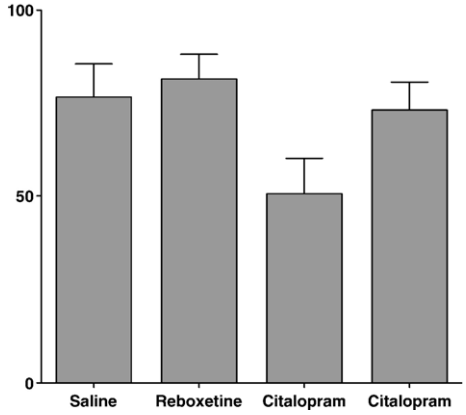


Fig. 1. Acute effect of the combined treatment with low-dose reboxetine (1 mg/kg) and citalopram (10 mg/kg) on freezing induced by conditioned fear. Drugs were administered s.c. 24 h after footshock and 4 h before conditioned fear stress. Freezing behavior (mean percentage±S.E.M.) scored during 5-min observation is shown. Behavior was sampled at 10-s intervals. Two-way ANOVA: effect of citalopram, $F(1, 60)=4.399$, $P=0.0402$; effect of reboxetine, $F(1, 60)=2.775$, $P=0.101$; effect of interaction, $F(1, 60)=1.168$, $P=0.2841$. $N=16$.

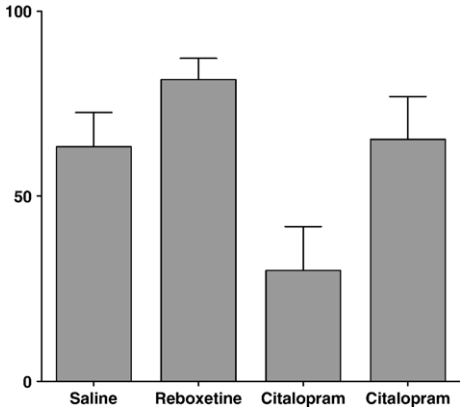


Fig. 2. Acute effect of the combined treatment with high-dose reboxetine (10 mg/kg) and citalopram (10 mg/kg) on freezing induced by conditioned fear. Drugs were administered s.c. 24 h after footshock and 4 h before conditioned fear stress. Freezing behavior (mean percentage±S.E.M.) scored during 5-min observation is shown. Behavior was sampled at 10-s intervals. Two-way ANOVA: effect of citalopram, $F(1, 28)=6.386$, $P=0.0174$; effect of reboxetine, $F(1, 28)=7.506$, $P=0.0106$; effect of interaction, $F(1, 28)=0.758$, $P=0.3913$. $N=8$.

### 3.4. Acute effect of reboxetine and citalopram on freezing in unshocked rats

To examine whether reboxetine increases freezing in a situation that is not associated with conditioned fear, the effect

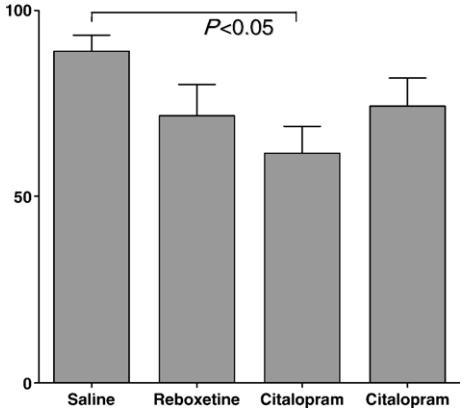


Fig. 3. Subchronic effect of the combined treatment with high-dose reboxetine (10 mg/kg) and citalopram (10 mg/kg) on freezing induced by conditioned fear. Drugs were administered s.c. once a day for 7 days from 24 h after footshock, and 4 h after the final injection rats were exposed to the shock chamber and the behavior was observed for 5 min. Freezing behavior (mean percentage±S.E.M.) scored during 5-min observation is shown. Behavior was sampled at 10-s intervals. Two-way ANOVA: effect of citalopram, $F(1, 60)=3.172$, $P=0.08$; effect of reboxetine, $F(1, 60)=0.099$, $P=0.7541$; effect of interaction, $F(1, 60)=4.584$, $P=0.0363$. $N=16$. $P$ values indicate the results of a post hoc test (Duncan's test).

of reboxetine on freezing in unshocked rats was tested and compared with that of citalopram. Freezing in unshocked rats was very low in contrast to that in rats exposed to conditioned fear. Acute reboxetine at doses of 1 and 10 mg/kg did not change freezing significantly, and acute citalopram did not change it [Percentage score of freezing behavior, saline controls, 8.3±6.0% ($N$=8); reboxetine 1 mg/kg 5.0±2.3% ($N$=8); reboxetine 10 mg/kg 14.6±5.4% ($N$=8); citalopram 1 mg/kg 6.7±6.7% ($N$=8); citalopram 10 mg/kg 11.3±5.2% ($N$=8); 1-way ANOVA, $F(4, 35)=0.514$, $P=0.7261$].

## 4. Discussion

This study examined the combined effects of the selective serotonin reuptake inhibitor citalopram and the selective noradrenaline reuptake inhibitor reboxetine on conditioned freezing, which is a sensitive animal model of fear, to detect the anxiolytic effect of selective serotonin reuptake inhibitors (Hashimoto et al., 1996; Inoue et al., 1996). In acute experiments, these drugs were administered 24 h after contextual fear conditioning by footshocks and 4 h before re-exposure to the shock chamber. This treatment schedule was chosen to detect the anxiolytic effects of drugs on conditioned fear. Drugs were administered before fear conditioning to examine the effects of drugs on emotional learning or perception of aversive stimuli (Inoue et al., 2000a,b). Consistent with our previous studies showing that clinically effective drugs for anxiety disorders reduce conditioned freezing when administered after fear conditioning and before re-exposure to the context (Hashimoto et al., 1996; Inoue et al., 1996, 2000a), we found that citalopram significantly decreased the expression of conditioned fear, assessed by using freezing as an index of fear. Interestingly, acute high-dose reboxetine administration increased conditioned freezing without increasing freezing in unshocked rats and counteracted the anxiolytic effect of a selective serotonin reuptake inhibitor.

Hashimoto et al. (1996) showed that noradrenaline reuptake inhibitors tended to increase conditioned freezing, but these effects were not statistically significant. In this study, high-dose reboxetine alone increased conditioned freezing more than did low-dose reboxetine alone, with a significant effect of reboxetine alone in 2-way ANOVA. Both low and high doses of acute reboxetine increase extracellular noradrenaline concentrations in the cortex markedly, and the effect of high-dose reboxetine is greater than that of low-dose reboxetine (Kitaichi et al., 2004). Preclinical evidence has suggested that increased noradrenergic function increases anxiety, and that an increased release of noradrenaline in the amygdala, hypothalamus and locus coeruleus participates in inducing anxiety and fear in response to stress (Tanaka et al., 2000). Noradrenergic activation in the amygdala, which has an essential role in the development and expression of conditioned fear (LeDoux, 2000), increases consolidation of conditioned fear memory (Lalumiere et al., 2003). Although we did not investigate whether direct noradrenaline infusion into the amygdala before the expression of conditioned fear increases freezing, it seems likely that the reboxetine-induced increase in extracellular noradrenaline in the brain, especially in the amygdala, increased conditioned freezing.

Inoue et al. (2004) showed that intra-amygdala injections of the selective serotonin reuptake inhibitor citalopram reduced the expression of conditioned freezing caused by a contextual stimulus. Together with the reproducible findings of this and previous studies (Hashimoto et al., 1996; Inoue et al., 1996; Li et al., 2001) showing that systemic administration of selective serotonin reuptake inhibitors reduces conditioned freezing, this reduction by citalopram supports the hypothesis that facilitation of serotonergic neurotransmission in the amygdala reduces conditioned fear and that an increase in extracellular serotonin after selective serotonin reuptake inhibitor administration has an anxiolytic action. This explains the results of this study: the increase in serotonin level in the brain (especially in the amygdala) after citalopram reduces conditioned freezing, and the increase in noradrenaline level after reboxetine counteracts the anxiolytic effect of citalopram and increases conditioned freezing by itself.

Subchronic reboxetine alone did not increase conditioned freezing itself and did not counteract the anxiolytic effect of citalopram significantly. Reboxetine injection increases extracellular noradrenaline levels similarly in rats chronically treated with reboxetine and saline (Sacchetti et al., 1999), but chronic reboxetine induces a down-regulation of β-adrenoceptors paralleled by desensitization of noradrenaline-coupled adenylate cyclase (Riva et al., 1989). Therefore, the postsynaptic, but not presynaptic, adaptive mechanism after chronic reboxetine treatment explains why subchronic reboxetine had no effect on conditioned freezing.

Historically, before the use of selective serotonin reuptake inhibitors, benzodiazepines and tricyclic antidepressants, which inhibit not only serotonin reuptake but also noradrenaline reuptake, were used to treat anxiety disorders (Erikkson and Humble, 1990; Inoue et al., 2000a; Zohar and Westenberg, 2000). Because of the higher rate of adverse events associated with tricyclic antidepressants and the potential for dependency associated with benzodiazepines, selective serotonin reuptake inhibitors are now a good first-line agent for anxiety disorders (Zohar and Westenberg, 2000). Serotonin–noradrenaline reuptake inhibitors have been examined for anxiolytic effects and have been approved for the treatment of some anxiety disorders (Allgulander et al., 2004; Meoni et al., 2004). The results of this study show that noradrenaline reuptake inhibition by serotonin–noradrenaline reuptake inhibitors can obstruct their anxiolytic action at least following acute treatment, but this obstructive action is not observed after chronic treatment. Further studies are necessary to clarify whether noradrenaline reuptake inhibition has therapeutic or adverse effects on anxiety in the treatment of anxiety disorders.

In conclusion, acute treatment with a noradrenaline reuptake inhibitor worsens conditioned freezing and weakens the anxiolytic effects of a serotonin reuptake inhibitor, but this anxiogenic effect of noradrenaline reuptake inhibition is not observed after subchronic treatment. These results suggest that adding a noradrenaline reuptake inhibitor to a serotonin reuptake inhibitor is not useful in reducing symptoms of

anxiety disorders but has adverse effects. However, this suggestion cannot ignore the possibility that noradrenaline reuptake inhibitors might be beneficial in treating other symptoms of anxiety disorders, such as depressive symptoms.

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