

TJS-010, a New Prescription of Kampo Medicine with Putative Antidepressive and Anxiolytic Properties. —A behavioral study using experimental models for depression and anxiety—

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ABSTRACT

We investigated the effect of TJS-010, a new prescription of Kampo or oriental medicine, on the locomotor activity and body temperature in rats in order to determine its antidepressive and anxiolytic effects. Tetrabenazine (TBZ), which sometimes induces depression in humans, decreased the spontaneous locomotion in rats, and attenuated the content of amines in several regions in the rat brain when intraperitoneally injected. TJS-010 was orally administered at a concentration of 750 mg/kg, and inhibited the locomotor suppression. The content of amines was not, however, altered. These results indicate that TJS-010 postsynaptically modulates the transmission or transduction. Imipramine, 5mg/kg, also enhanced locomotion in TBZ-treated rats, which was similar to the effect of TJS-010. These results suggest that TJS-010 has an antidepressive effect. TJS-010 also facilitated the hypothermia induced by subcutaneous injection of 0.1 mg/kg (\pm)-8-hydroxy-2-(di-N-propylamino)tetralin (8-OH-DPAT), which is known to be mediated by serotonin-1A receptors. The hypothermia in the rats via an activation of serotonin-1A receptors is often observed with anxiolytic drugs. These results may raise the possibility that TJS-010 has an anxiolytic property. TJS-010 may serve as a useful drug for the treatment of those who suffer from depressive and anxiety disorders.

Key words: *Depression, Anxiety, Kampo*

Many psychotropic drugs such as neuroleptics, antidepressants and anxiolytics have been introduced into clinical practice from 1950s and their efficacy in the treatment of those who suffer from psychiatric disorders has been widely accepted. These drugs, however, sometimes induce unpleasant side effects.

Several kinds of traditional oriental medicine (Kampo) have been reported to possess psychotropic actions. For example, Saiko-ka-ryukotsu-bo-rei-to is effective with few side effects in those who are in a state of anxiety or depressive mood²⁰. Shimotsu-to improves the cognitive function and memory in rats²⁷. Moreover, Untan-to is often used to treat patients who suffer from anxiety, depressive mood and insomnia. Detailed mechanisms of action of Kampo, however, are still unknown. TJS-010, a new prescription of Kampo, is composed of Hange (pinelliae tuber), Bukuryou (hoelen), Chimpi (aurantii nobilis pericarpium), Chikujo (phyllostachysis caulis in taeniam), Kijitsu (aurantii fructus immaturus), Kanzou (glycyrrhizae radix) and Shoukyou (zingiberis rhizoma). The composition of TJS-010 is

similar to that of Untan-to. This similarity suggests to us of the possibility of TJS-010 for a new antidepressant or anxiolytic drug.

Tetrabenazine (TBZ) provides an animal model of depression because TBZ is known to precipitate human subjects into depression¹⁰. It induces the release of monoamines such as dopamine, norepinephrine and serotonin into the synaptic cleft to cause a decreased level in the brain^{17,22,29,30}, and leads to a decrease in locomotor activity^{6,22}. Several antidepressant drugs improve the TBZ-induced depletion of monoamine concentration in the brain and behavioral depression^{6,29,30}.

Some kinds of anxiolytics such as buspirone, ipsapirone and gepirone have recently been proved to be partial agonists for serotonin-1A receptors^{18,23}, suggesting that the agonistic effect on serotonin-1A receptors is responsible for their anxiolytic properties. Agonists for serotonin-1 receptors also induce hypothermia in rats and the reduction in body temperature is known to be functionally mediated by serotonin-1A receptors in the central nervous system^{24,25}.

In this study, we have investigated whether

TJS-010 has effects similar to those of antidepressants or anxiolytics, using TBZ-induced suppression of locomotion and serotonin-1A receptor agonist (\pm)-8-hydroxy-2-(di-N-propylamino)tetralin (8-OH-DPAT)-induced hypothermia.

MATERIALS AND METHODS

Animals: Male Wistar rats weighing 150–220g were obtained from Hiroshima Laboratory Animals. Rats were housed in cages with free access to food and water in an air-conditioned room. They were subjected to a 12 hour light/dark cycle (light on; 8:30–20:30).

Administration of drugs: In the TBZ experiments, rats were intraperitoneally injected with indicated concentrations of TBZ and locomotion was measured immediately. TJS-010 (generously donated by Tsumura & Co.) was orally administered 30 min before the injection of TBZ. Imipramine was also orally administered 30 min before the injection of TBZ. Rats were subcutaneously injected with indicated concentrations of 8-OH-DPAT. TJS-010 was orally administered 90 min before the injection of 8-OH-DPAT.

Measurement of spontaneous locomotor activity: Behavior was measured between 9:30–17:00, using 2 machines (Animex III-A) simultaneously. Spontaneous locomotor activity was measured for indicated duration and calculated with a PT-2 activity meter.

Measurement of amine contents in rat brain: Rats were sacrificed by decapitation and their brains were stocked at -80°C until measurement of amine contents. The brains were dissected into frontal cortex (FC), striatum (ST) and thalamus/hypothalamus (TH/HT). The tissue was homogenized with 0.1 N PCA and 1 mM EDTA, and centrifuged at 12000 rpm for 15 min. An aliquot of supernatant was then filtrated through a chromatodisc (pore size $0.2\ \mu\text{m}$) and the level of monoamines determined by high performance liquid chromatography with electrochemical detection. The mobile phase was 50 mM phosphate buffer (pH 3.2) containing 10 % methanol and 0.85 mM octanesulfonic acid.

Measurement of body temperature: Body temperature was measured before the injection of 8-OH-DPAT, and 15 min after the injection, with a thermometer inserted into rectum.

Statistical analysis: Statistical analysis was performed by Student's-t test.

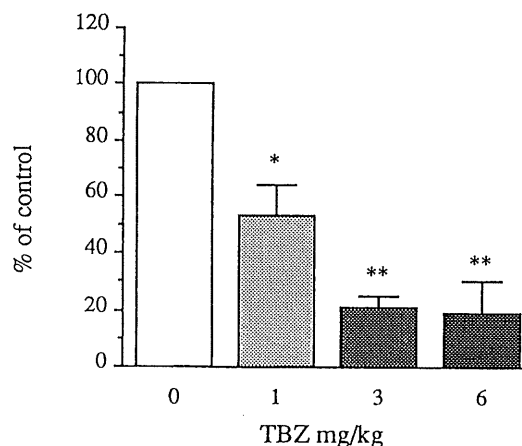


Fig. 1. Effect of tetrabenazine on spontaneous locomotor activity in rats

Rats were intraperitoneally injected with indicated concentrations of TBZ and immediately locomotion was measured for 60 min. Data are expressed as % of control. $n=4-8$. Control rats showed the activity of 896 ± 85 counts/60min.

* $p < 0.05$, ** $p < 0.01$ vs control.

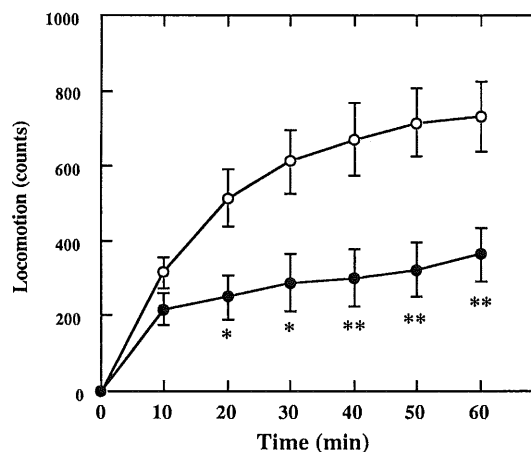


Fig. 2. Time course of tetrabenazine-induced suppression of locomotion in rats

Rats were treated with 1mg/kg tetrabenazine and the locomotion was measured for 60 min. $n=8$. open circle: control rats, closed circle: TBZ-treated rats * $p < 0.05$, ** $p < 0.01$ vs control.

RESULTS

Effect of TBZ on spontaneous locomotion in rats

TBZ induced the depletion of spontaneous locomotor activity in rats. Fig. 1 shows the dose-dependent inhibition of locomotor activity induced by TBZ within 60 min. Intraperitoneal injection with 1 mg/kg TBZ attenuated the locomotion approximately 50 % of control, and 3 and 6 mg/kg TBZ diminished the locomotor activity to about

20 %. The injection of 1 mg/kg TBZ rapidly decreased the locomotion and the inhibition was obvious after 20 min (Fig. 2).

Effect of TJS-010 and imipramine on the locomotion in TBZ-treated rats

TJS-010, when administered alone, did not change locomotor activity (data not shown). However, TJS-010, at a dose of 750 mg/kg, partly reversed behavioral sedation induced by 1 mg/kg TBZ. The reversal effect of accumulated locomotion for 60 min by TJS-010 was significant (Fig. 3). The locomotion after treatment with TJS-010 was 141.6 ± 7.7 % of TBZ-injected control rats.

Imipramine (5 mg/kg) was orally administered

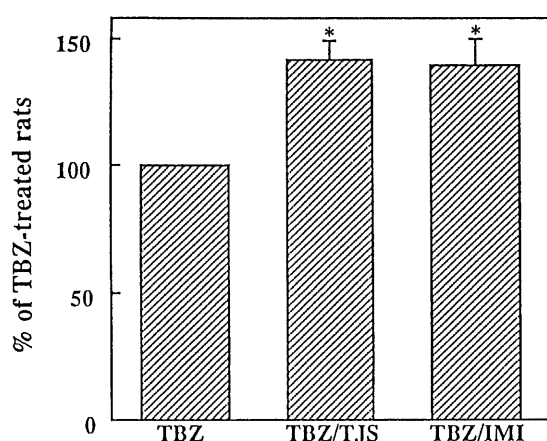


Fig. 3. Effect of TJS-010 and imipramine on tetra-benzazine-induced suppression of locomotion in rats. Rats were orally administered 750 mg/kg TJS-010 (TJS) (n=15) or 5 mg/kg imipramine (IMI) (n=9). After 30 min, rats were treated with 1 mg/kg tetra-benzazine and the locomotion was measured for 60 min. * $p < 0.05$, vs TBZ

and the locomotion was measured. Imipramine significantly reversed the sedation of locomotion induced by TBZ (Fig. 3). The locomotion after treatment with imipramine was 139.2 ± 10.5 % of TBZ-injected control rats. Imipramine (5 mg/kg) did not alter activity in naive rats (data not shown).

Amine contents in rat brain

The concentration of brain monoamines was determined 120 min after the rats were treated with 1 mg/kg TBZ. Treatment with 1 mg/kg TBZ attenuated the content of norepinephrine in the FC and TH/HT, of dopamine in ST and TH/HT, and of serotonin in TH/HT (Table 1).

The monoamine content was also determined after administration of TJS-010 or imipramine in the region where TBZ decreased monoamines. Norepinephrine content did not change by TJS-010 or imipramine administration in FC or TH/HT of rat brain (Fig. 4). Either dopamine in ST or TH/HT (Fig. 5), or serotonin in TH/HT (Fig. 6) did not change by TJS-010 or imipramine administration.

Effect of TJS-010 on hypothermia induced by 8-OH-DPAT in rats

Rats were injected with 8-OH-DPAT subcutaneously, and their body temperature was measured. As shown in Fig. 7, 8-OH-DPAT decreased the body temperature 15 min after the injection in a dose-dependent manner. TJS-010 (750 mg/kg) significantly enhanced the hypothermia induced by 0.1 mg/kg 8-OH-DPAT 15 min after the injection when it was orally administered 90 min before the injection (Fig. 8). Decrease in temperature induced by 0.1 mg/kg 8-OH-DPAT was 1.65 ± 0.26 or 0.89 ± 0.15 °C with or without TJS-010, respectively.

Table 1. Effect of TBZ on monoamine concentration on various regions of rat brain

Region	Treatment	Monoamine (nmol/g tissue)		
		norepinephrine	dopamine	serotonin
FC	control	0.13 ± 0.01	0.07 ± 0.02	0.80 ± 0.09
	TBZ	$0.06 \pm 0.03^*$	0.08 ± 0.02	0.63 ± 0.04
ST	control	0.29 ± 0.02	11.39 ± 1.11	1.27 ± 0.11
	TBZ	0.31 ± 0.04	$5.00 \pm 0.57^{**}$	1.15 ± 0.07
TH/HT	control	1.03 ± 0.05	0.53 ± 0.06	1.79 ± 0.09
	TBZ	$0.81 \pm 0.07^*$	$0.24 \pm 0.02^{**}$	$1.44 \pm 0.13^*$

Rats were injected without or with 1 mg/kg TBZ intraperitoneally and after 2 hours the content of monoamine was determined as described in method.

Each value is the mean \pm S.E.M. for 8 rats. Statistical analysis was performed by Student's t test. * $p < 0.05$, ** $p < 0.01$ compared with control.

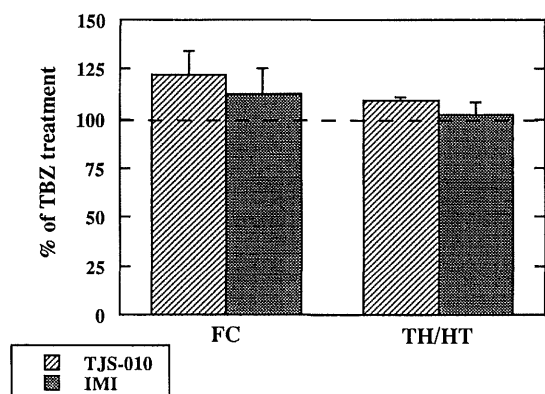


Fig. 4. Norepinephrine content in TBZ-treated rat brain

Rats were orally administered 750mg/kg TJS-010 (n=15) or 5mg/kg imipramine (IMI) (n=9) 30 min before injection of 1mg/kg TBZ. Norepinephrine content was measured 90 min after the injection. Data are expressed as % of norepinephrine content in each region of TBZ-treated rats without administration of TJS-010 or imipramine (0.29 ± 0.06 and 2.31 ± 0.35 nmol/g tissue in FC and TH/HT, respectively). Vertical bars represent S.E.M.

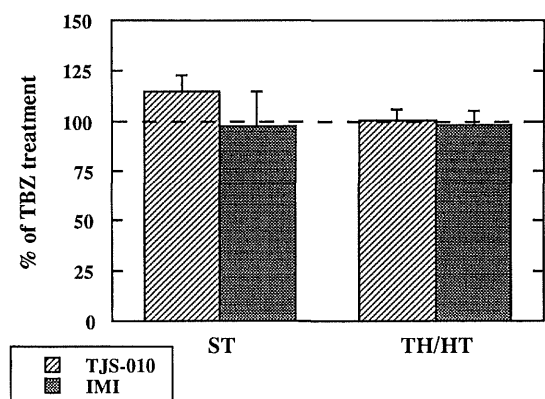


Fig. 5. Dopamine content in TBZ-treated rat brain Rats were orally administered 750mg/kg TJS-010 (n=15) or 5mg/kg imipramine (IMI) (n=9) 30 min before injection of 1mg/kg TBZ. Dopamine content was measured 90 min after the injection. Data are expressed as % of dopamine content in each region of TBZ-treated rats without administration of TJS-010 or imipramine (5.92 ± 1.09 and 0.36 ± 0.04 nmol/g tissue in ST and TH/HT, respectively). Vertical bars represent S.E.M.

DISCUSSION

TBZ reduced the spontaneous locomotor activity in rats, as reported in previous papers^{6,22}, but the decrease in activity was apparent more rapidly and at lower doses. We injected rats in daylight whereas rats in previous investigations^{6,22} were injected during dark periods. Rats appear to be more sensitive to TBZ at light period.

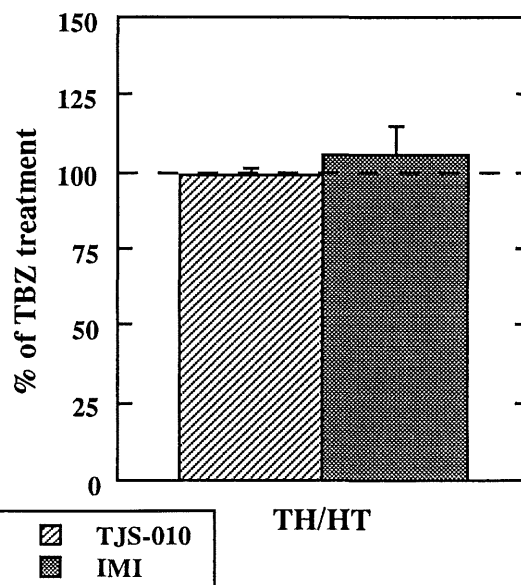


Fig. 6. Serotonin content in TBZ-treated rat brain Rats were orally administered 750mg/kg TJS-010 (n=15) or 5mg/kg imipramine (IMI) (n=9) 30 min before injection of 1mg/kg TBZ. Serotonin content was measured 90 min after the injection. Data are expressed as % of serotonin content of TBZ-treated rats without administration of TJS-010 or imipramine (1.99 ± 0.10 nmol/g tissue in TH/HT). Vertical bars represent S.E.M.

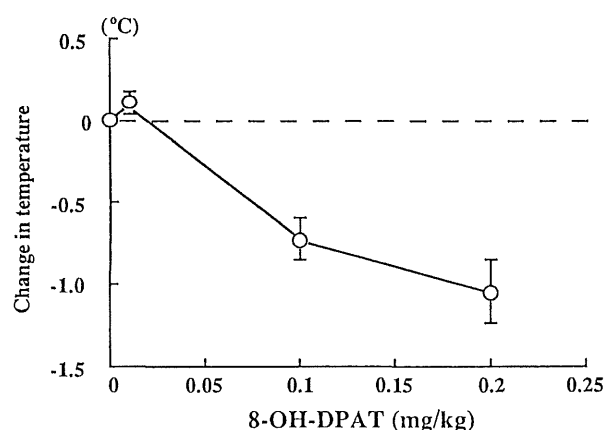


Fig. 7. Effect of 8-OH-DPAT on change in body temperature in rats

Rats were subcutaneously injected with various doses of 8-OH-DPAT, and after 15 min the temperature was measured. Data are expressed as change in temperature between post-injection and pre-injection. Each value shows the mean of 6 rats. Vertical bars represent S.E.M.

5-Hydroxytryptophan(5-HTP), a precursor of serotonin, is known to inhibit a spontaneous locomotor activity as well and this effect might be due to the excess of serotonin in the synaptic

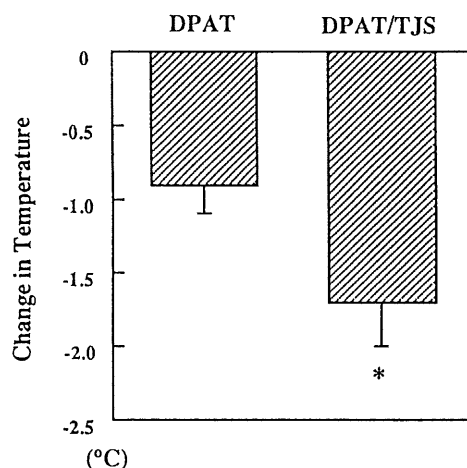


Fig. 8. Effect of TJS-010 on 8-OH-DPAT-induced hypothermia in rats

Rats were orally administered with 750 mg/kg TJS-010, and after 90 min they were injected with 0.1 mg/kg 8-OH-DPAT. Data are expressed as change in temperature between post-injection and pre-injection. Each value shows the mean of 12 rats. Vertical bars represent S.E.M. * $p < 0.05$ compared with 8-OH-DPAT-treated rats.

cleft¹⁴). The facilitation of serotonin transmission may be responsible at least in part for the attenuation of the locomotion induced by TBZ in rats as a previous report has suggested²²). The possibility of supersensitivity in serotonin transmission of affective disorders is documented using human platelets^{13,28}) and response to hormones¹²). However, by further investigation it is important to clarify which amine is more important for behavioral depression induced by TBZ.

TJS-010 significantly reversed TBZ-induced decrease in spontaneous locomotor activity in rats. Imipramine, a prototype of tricyclic antidepressant, also inhibited the effect of locomotion by TBZ. Hori and his colleagues reported that imipramine antagonizes TBZ-induced suppression of behavior in rats⁶). Nagayama et al¹⁴) have suggested that mianserin, an antidepressant, improves the 5-HTP-induced suppression of locomotor activity. Effect of TJS-010 on the locomotion appears similar to those of antidepressants, which suggests that TJS-010 may have an antidepressive effect on human patients. However, the mechanism of antidepressants has not been fully elucidated. Tricyclic antidepressants including imipramine have a moderate effect in blocking serotonin-2 receptors²⁶) as well as in serotonin uptake inhibition. Based upon the result that TJS-010 or imipramine did not alter the content of amines, we may postulate that TJS-010 may change a postsynaptic neural transmission or transduction and reverse the decrease in locomotor activity by TBZ. The effect of imipramine

on the locomotion in this study may be mediated partly through a postsynaptic event as well. It is necessary to investigate the relationship between behavioral change and neurochemical findings including the metabolism of amines.

Patients with anxiety disorders, especially panic disorder, have low responsivity of serotonin-1A receptor-mediated hypothermic and neuroendocrine responses⁸). A large body of literature is available on the efficacy of azapirones such as buspirone, ipsapirone and gepirone, in anxiety disorder^{1-5,7}). Azapirones are presumably especially suitable for chronic anxiety patients as they do not result in an abuse, addiction, dependence or withdrawal symptom^{15,16,19}) which often occurs in benzodiazepine treatment. Azapirones show direct effect on serotonin-1A receptors¹⁸) and the effect seems important for the treatment of anxiety. It has been established that 8-OH-DPAT-induced hypothermia is mediated by postsynaptic serotonin-1A receptors²⁵). The thermoregulation by azapirones is related to their effectiveness as anxiolytics⁹). In this regard, it should be noted that in this study TJS-010 significantly enhanced 8-OH-DPAT-induced hypothermia. This raises the possibility that TJS-010 has putative anxiolytic property. The exact mechanism of action sites of TJS-010 on serotonin-1A receptor functions is not yet understood. TJS-010 may act on the 8-OH-DPAT recognition site of the receptor directly, facilitate the binding capacity allosterically, or increase the responsivity of the postreceptor messenger systems.

The dosage of TJS-010 used in this study is 3 to 5 folds of the clinical dosage, which appears appropriate in order to expect an antidepressive or anxiolytic effect clinically, judging from the clinical dosage of imipramine.

TJS-010 is composed of Hange (pinelliae tuber), Bukuryou (hoelen), Chimpi (aurantii nobilis pericarpium), Chikujo (phyllostachysis caulis in tainiam), Kijitsu (aurantii fructus immaturus), Kanzou (glycyrrhizae radix) and Shoukyou (zingiberis rhizoma). Some of them show CNS effects such as respiration and convulsion: immune systems and intracellular signaling systems^{11,21}) which may, at least in part, contribute to the reversal effect of TJS-010 on TBZ-induced suppression of the locomotion and synergistic effect of hypothermia induced by 8-OH-DPAT. TJS-010 is a newly prescribed medicine and is expected to improve depressive or anxious states. The present findings indicate that TJS-010 inhibits the effect of TBZ and enhances the effect of 8-OH-DPAT, which may suggest that TJS-010 possibly has antidepressive and anxiolytic action.

In conclusion, in this study we have demonstrated that 1)TBZ decreased the spontaneous locomotion in rats and TJS-010 antagonized the behavioral suppression induced by TBZ, and that

2)8-OH-DPAT reduced the body temperature of rats and TJS-010 facilitated the hypothermia induced by 8-OH-DPAT. These results suggest a possibility that TJS-010 show antidepressive and anxiolytic effects.

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