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Dipeptide Tyr-Leu (YL) exhibits anxiolytic-like activity after oral administration via activating serotonin 5-HT_{1A}, dopamine D_1 and $GABA_A$ receptors in mice

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ABSTRACT

We found that Tyr-Leu (YL) dose-dependently exhibits potent anxiolytic-like activity (0.1–1 mg/kg, i.p.) comparable to diazepam in the elevated plus-maze test in mice. YL was orally active (0.3–3 mg/kg). A retro-sequence peptide or a mixture of Tyr and Leu was inactive. The anxiolytic-like activity of YL was inhibited by antagonists for serotonin 5-HT_{1A}, dopamine D_1 and $GABA_A$ receptors; however, YL had no affinity for them. We also determined the order of their activation is 5-HT_{1A}, D_1 and $GABA_A$ receptors using selective agonists and antagonists. Taken together, YL may exhibit anxiolytic-like activity via activation of 5-HT_{1A}, D_1 and $GABA_A$ receptors.

1. Introduction

It has been reported that low molecular weight peptides consisting of 3–7 L-amino acids sometimes exhibit anxiolytic-like activities after oral administration in behavioral pharmacological tests in mice. A number of bioactive peptides have been isolated from enzymatic digests of food proteins. Among them, rubiscolin-6 (YPLDLF), a δ opioid peptide derived from the large subunit of spinach d-ribulose-1,5-bisphosphate carboxylase/oxygenase (Rubisco), showed anxiolytic-like activities at a dose of 100 mg/kg after oral administration in the elevated plus-maze test in mice [1,2]. Orally administered soymorphin-5, 6 and 7 (YPFVV, YPFVVN and YPFVVNA, respectively), μ opioid peptides derived from soy β-conglycinin had anxiolytic-like activity at a dose of 10–30 mg/kg in mice [3]. Rubimetide (MRW), a hypotensive and vasorelaxing tripeptide derived from Rubisco, exhibited anxiolytic-like activity at a dose of 1 mg/kg after oral administration [4]. In the current study, we found that tyrosyl leusine (YL) had potent anxiolytic-like activity after oral administration at a lower dose than previously reported anxiolytic-like peptides [1–4]. We then investigated the mechanism of the anxiolytic-like activity of YL.

It was known that serotonin 5-HT_{1A} receptor, dopamine D_1 receptor, and γ-amino butyric acid type A ($GABA_A$) receptor played an important key role in anxiolytic-like activity [1,5–7]; therefore, we tested whether the anxiolytic-like activity of YL is mediated by activation of these receptors. Furthermore, we determined the order of activation of 5-HT_{1A}, D_1 and $GABA_A$ receptors in anxiolytic-like activity using agonists and antagonists for them.

2. Materials and methods

2.1. Animals

Four–six-week-old male ddY mice at 20–24 g or 26–30 g body weight for intracerebroventricular (i.c.v.) or intraperitoneal (i.p.) and oral (p.o.) administration, respectively, were obtained from SLC (Shizuoka, Japan). Seven-week-old mice were also used for i.p. administration. All animals were housed in a temperature-controlled room (23 °C) on a 12-h light–dark cycle with lights on at 07:00. All animals had free access to food pellets and water. All experiments were approved by the Kyoto University Ethics Committee for Animal Research Use. All animals were euthanized by an overdose of anesthesia drugs after the experiment.

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2.2. Reagents

Tyr-Leu (YL), Tyr-Ile (YI), Leu-Tyr (LY), Ile-Tyr (IY) and Leu-Tyr-Leu (LYL) were obtained from Bachem AG (Bufendorf, Switzerland). Tyr-Leu-Tyr (YLY) and Tyr-Leu-Gln (YLQ) were synthesized by F-moc strategy. Amino acids Tyr and Lue were purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan). WAY100135 dihydrochloride, a serotonin 5-HT_{1A} receptor antagonist; R(+)-SCH-23390 hydrochloride, a dopamine D_1 receptor antagonist; (−)-bicuculline, γ-amino butyric acid $(GABA)_A$ receptor antagonist; 8-hydroxy-DPAT hydrobromide, a serotonin 5-HT_{1A} receptor agonist; SKF38393, a dopamine D_1 receptor agonist; were obtained from Tocris Bioscience (Bristol, UK). Muscimol, a $GABA_A$ receptor agonist, and diazepam were purchased from Sigma–Aldrich Inc. (St. Louis, MO).

2.3. Elevated plus-maze test

Anxiolytic-like behavior was measured using the elevated plus-maze (EPM) test, which was performed as described previously [1,3,4,8–10]. Four arms (25 cm long × 5 cm wide) were placed 50 cm above the ground. Two opposite arms were delimited by acrylic vertical walls (15 cm high, closed arms), whereas the other two, opposite arms had unprotected edges (open arms). A mouse was placed in the center of the maze facing an open arm and observed for 5 min to measure the cumulative time and frequency of entries into open and closed arms. Arm entry was defined as the entry of four paws into an arm. Open-arm entry time (time spent in open arms) was expressed as a percentage of the total entry time (% of time), and the number of open-arm entries was expressed as a percentage of the number of total entries (% of visit). Peptides or amino acids dissolved in saline were i.p. administered 30 min before the test. Diazepam was also dissolved in saline by sonication. Antagonists were i.p. co-administered with peptide 30 min before the test. YL in saline was also administered by gavage. The total number of visits to open and closed arms, and the cumulative time spent in open and closed arms were measured on a monitor through a video camera system. The data were checked by observers unaware of the experimental groups. The EPM test was started at 11:00 a.m. during the light phase of the light/dark cycle.

2.4. Open-field test

The open-field test was performed as previously described with slight modification [11]. The apparatus consisted of a circular arena of 60 cm diameter and wall height of 50 cm. The apparatus was gray with black lines on the bottom, which divided the open-field into 25 parts of similar area by two concentric circles as a series of radii. Each mouse was placed in the center circle and its movement monitored through a video camera system for 5 min. The time spent in the center circle was measured. The open-field test was started at 11:00 a.m.

2.5. Intracerebroventricular (i.c.v.) administration

I.c.v. administration was performed as described previously [12–14]. Briefly, a 28-gauge stainless steel needle attached to a 0.05-ml Hamilton syringe was inserted perpendicularly through the skull into the brain. The site of injection was 2 mm from either side of the midline on a line drawn through the anterior base of the ears (the lateral ventricle). YL was dissolved in artificial cerebrospinal fluid (ACSF: 138.9 mM NaCl, 3.4 mM KCl, 1.3 mM $CaCl_2$, 4.0 mM $NaHCO_3$, 0.6 mM NaH_2PO_4, 5.6 mM glucose, pH 7.4). Four microliters of YL solution was i.c.v. administered 20 min before the test.

2.6. Statistical analysis

All values are expressed as the means ± S.E.M. Analysis of variance (ANOVA) followed by Fisher's test was used to assess differences among groups. *P* values less than 0.05 were considered significant.

3. Results

3.1. Dipeptide YL exhibits potent anxiolytic-like activity after oral administration

We tested whether dipeptide YL and its related peptides exhibited anxiolytic-like activity after i.p. administration in the elevated plus-maze test and open-field test in mice. Initially we investigated anxiolytic-like activity of Ile-Tyr (IY), which is an ACE inhibitory peptide with anti-hypertensive activity, since ACE inhibitors sometimes show anxiolytic-like activity [15]. IY at a dose of 30 mg/kg exhibited anxiolytic-like activity after i.p. administration in the elevated-plus maze test in mice (Supplementary Fig. S1). After preliminary experiments using IY analogues, we finally found that YL has anxiolytic-like activity at a lower dose than the minimum effective dose of IY.

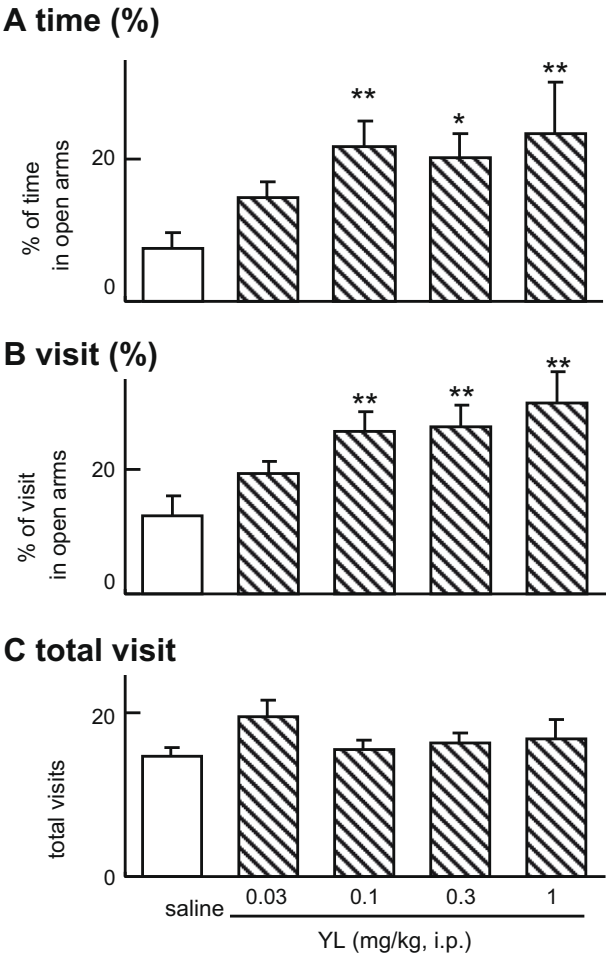

Fig. 1. Anxiolytic-like activity of YL after i.p. administration in the elevated plus-maze test in mice. YL at a dose of 0.03–1 mg/kg was i.p. administered 30 min before the tests. The percentages of time (A) and visits (B) spent in the open arms, and total visits (C) to both open and closed arms during the test for 5 min were measured. Each value is expressed as the means ± S.E.M. ($n = 5–8$). $^{*}P < 0.05$, $^{**}P < 0.01$, compared with the saline-treated control group.

YL at doses of 0.1–1.0 mg/kg (0.34–3.4 μmol/kg) dose-dependently increased the percentage of the time and visits in open arms for 5 min in the elevated plus-maze test using five–six-week-old mice at 26–30 g, but had no significant effect on total entry number (Fig. 1). Seven-week-old mice at 34–36 g also showed anxiolytic-like activity after i.p. administration of YL (Supplementary Fig. S2). In the open-field test, YL at a dose of 0.1 mg/kg (i.p.) increased time spent and visits in the center circle; however, locomotor activity was not affected (Table 1). Thus, we demonstrated that YL exhibits anxiolytic-like activity after i.p. administration by two paradigms. The minimum effective dose of YL in the elevated plus-maze test was 0.1 mg/kg, which was comparable to the anxiolytic. Indeed, the anxiolytic-like activity of YL tended to be more potent than that of diazepam, a representative anxiolytic, compared at the same doses (1 mg/kg, i.p.), as shown in Fig. 2A. A mixture of constitutive amino acids Tyr and Leu at a dose of 3.4 μmol/kg equal mole to 1 mg/kg of YL was inactive (Fig. 2B). LY, a retro-sequence dipeptide of YL, at a dose of 0.1–1 mg/kg was also inactive (Fig. 2C), suggesting that the amino acid sequence of YL is important for potent anxiolytic-like activity. YI, a dipeptide with substitution of the branch chain amino acid Leu in YL for Ile, and IY, its retro-sequence peptide, were also inactive at a dose of 0.1–1 mg/kg (Fig. 2C). The ACE inhibitory activity of YL (IC_{50} = 109 μM) was lower than that of IY (IC_{50} = 3.4 μM), suggesting that the anxiolytic-like activity of YL is independent of ACE inhibitory activity.

For tripeptides containing the YL sequence, YLY and YLQ (0.3–1 mg/kg, i.p.) had anxiolytic-like activity; however, LYL was inactive (Fig. 2D). Taken together, the N-terminal site of YL may be quite important for anxiolytic-like activity, and its C-terminal elongation might be tolerated.

Orally administered YL (0.3–3.0 mg/kg equal to 1.0–10 μmol/kg) increased the percentage of time in open arms of the maze (Fig. 3A). Furthermore, centrally administered YL (0.1 nmol/mouse) had anxiolytic-like activity (Fig. 3B). YL did not change the total visits after oral and i.c.v. administration (data not shown), indicating that YL did not affect locomotor activity. Thus, we demonstrated that orally administered YL has potent anxiolytic-like activity in mice.

3.2. Anxiolytic-like activity of YL was mediated via activation of serotonin 5-HT_{1A}, dopamine D_1 and $GABA_A$ receptors

We investigated the mechanism underlying the anxiolytic-like activity of YL. 5-HT_{1A}, D_1 and $GABA_A$ receptors are known to be associated with anxiolytic-like activity in animals and humans [1,5–7]; thus, we investigated whether these receptors were involved in the anxiolytic-like activity of YL using antagonists for them.

The anxiolytic-like activity of YL (1 mg/kg, i.p.) was significantly blocked by i.p. pretreatment of WAY100135 (10 mg/kg), SCH23390 (30 μg/kg), bicuculline (5 mg/kg) or flumazenil (1 mg/kg), an antagonist for 5-HT_{1A} receptor, D_1 receptor, the GABA site of $GABA_A$ receptor or its benzodiazepine site, respectively (Fig. 4). No antagonists used in this study had any effect on anxiety-related behavior in the elevated plus-maze test under our experimental conditions (Fig. 4B and Supplementary Fig. S3). These results suggest that the anxiolytic-like activity of YL is mediated by 5-HT_{1A}, D_1 and $GABA_A$ receptors. Furthermore, the affinity of YL for 5-HT_{1A} and D_1 receptors, and GABA or benzodiazepine sites of $GABA_A$ receptor at 100 μM were negligible (Supplementary Table S1). These results suggest that YL exhibits anxiolytic-like activity via the release of neurotransmitters, including serotonin, dopamine and GABA, and the activation of 5-HT_{1A}, D_1 and $GABA_A$ receptors.

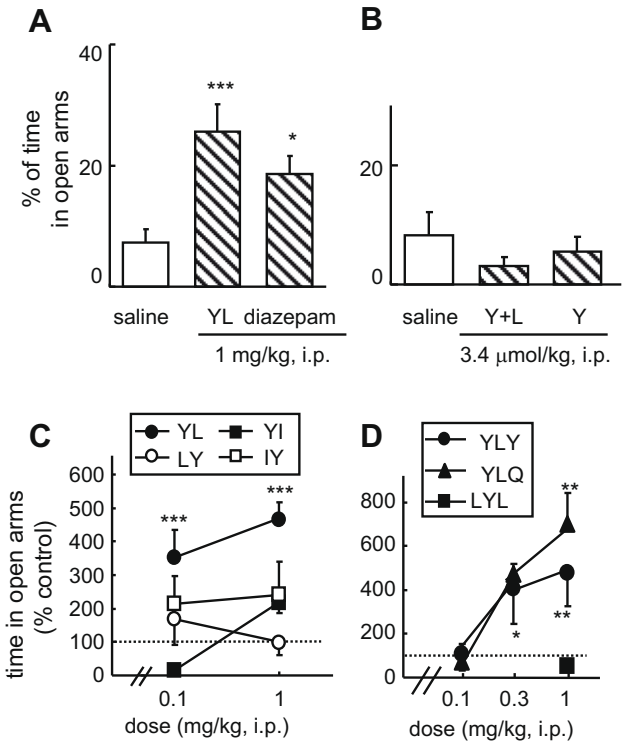

Fig. 2. Comparison of the anxiolytic-like activities of YL, its derivatives and diazepam. They were i.p. administered 30 min before the tests. The anxiolytic-like activities induced by diazepam (A, 1 mg/kg), Tyr alone or a mixture of the constitutive amino acids Tyr and Leu (B, 3.4 μmol/kg equimolar to 1 mg/kg of YL), YL-related dipeptides (C), or tripeptides (D, 0.1–1 mg/kg) were measured in the elevated plus-maze test in mice. Each value is expressed as the means ± S.E.M. (A, n = 12; B, n = 5; C, n = 3–8; D, n = 3–9). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, compared with each group.

3.3. Novel anxiolytic pathway via 5-HT_{1A}, D_1 and $GABA_A$ receptors

We investigated how these receptors were activated in emotional regulation using agonists and antagonists selective for them. The increase in the % of time in open arms by 8-OH-DPAT (1 mg/kg, i.p.), an agonist for 5-HT_{1A} receptor, was blocked by SCH23390 or bicuculline, an antagonist for D_1 or $GABA_A$ receptors, respectively (Fig. 5A). The anxiolytic-like activity of SKF38393 (1 mg/kg, i.p.), an agonist for D_1 receptor, was inhibited by bicuculline, but not by WAY100135 (Fig. 5B). The anxiolytic-like activity of muscimol (0.3 mg/kg, i.p.), an agonist for $GABA_A$ receptor, was inhibited by neither WAY100135 nor SCH23390 (Fig. 5C). Taken together, 5-HT_{1A} receptor activation may induce dopamine release and D_1 receptor activation followed by GABA release and $GABA_A$ receptor activation, probably in the central nervous system (CNS). Thus, we hypothesized that YL induced serotonin release and 5-HT_{1A} receptor activation followed by the activation of D_1 and $GABA_A$ receptors, as shown in Fig. 5D.

Table 1
Anxiolytic-like activity of YL in open-field behaviors.

	Saline	YL
% of time in center circle	0.889 ± 0.318	2.06 ± 0.234*
% of visits in center circle	1.53 ± 0.428	3.02 ± 0.404*
Locomoter activity	187 ± 13.4	189 ± 22.2

Results are expressed as the means ± S.E.M. (n = 6).
* $P < 0.05$, compared with the saline-treated control group.

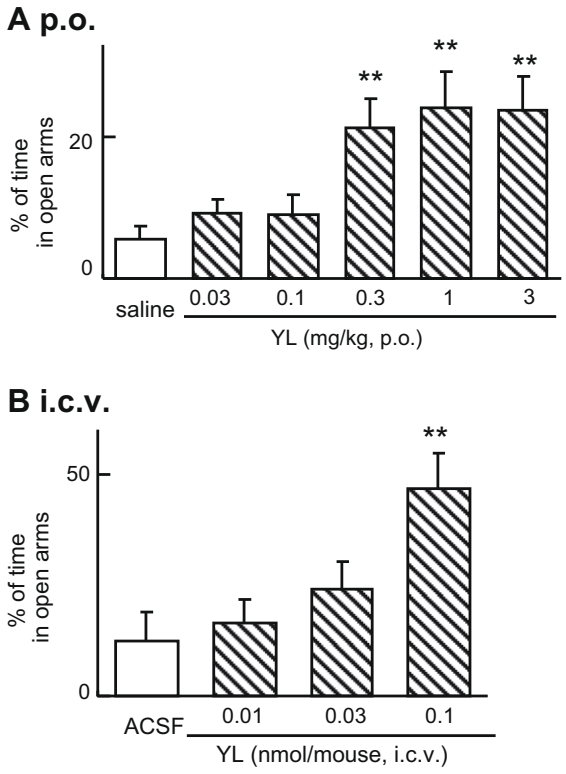

Fig. 3. Anxiolytic-like activity of YL after oral (A) or i.c.v. (B) administration in the elevated plus-maze test in mice. YL at a dose of 0.03–3 mg/kg or 0.01–0.1 nmol/mouse was orally or i.c.v. administered 30 (p.o.) or 20 (i.c.v.) min before the tests, respectively. Each value is expressed as the means ± S.E.M. (A, n = 5–14; B, n = 7–9). $^{**}P < 0.01$ compared with the saline- or ACSF-treated control group.

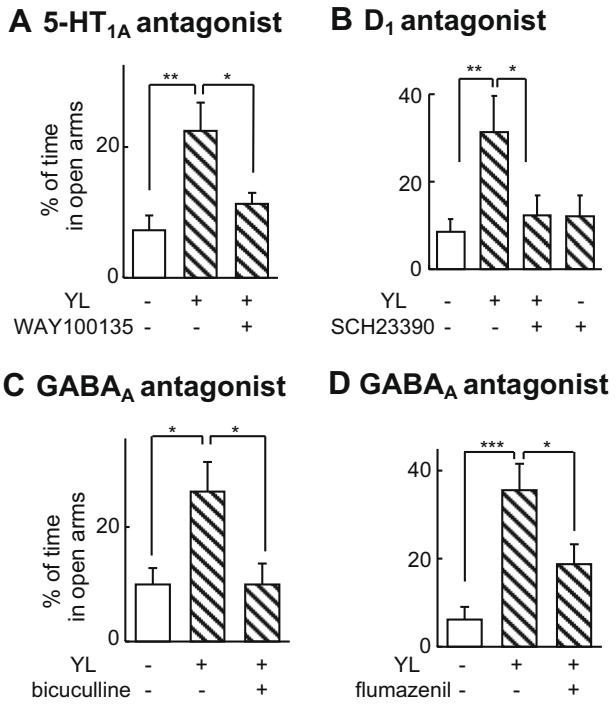

Fig. 4. Effects of antagonists for serotonin 5-HT_{1A} (A) dopamine D_1 (B) and $GABA_A$ receptors (C and D) on anxiolytic-like activity of YL. YL (1.0 mg/kg) was i.p. co-administered with WAY100135 (10 mg/kg), SCH23390 (30 μg/kg), bicuculline (5 mg/kg) and flumazenil (1 mg/kg), antagonists selective for 5-HT_{1A} receptor, D_1 receptor, the GABA site of $GABA_A$ receptor, and its benzodiazepine site, respectively, 30 min before the tests. Each value is expressed as the means ± S.E.M. (n = 5–12). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with each group.

4. Discussion

We found for the first time that dipeptide YL had potent anxiolytic-like activity comparable to diazepam in the elevated plus-maze test in mice. The amino acid sequence of YL was essential for potent anxiolytic-like activity. YL was orally active, and the minimum effective dose for anxiolytic-like activity after oral administration (0.3 mg/kg) was threefold higher than that after i.p. administration (0.1 mg/kg). The constitutive amino acid mixture was inactive. The anxiolytic-like activity after oral administration might be explained by resistance to digestive protease in the gastrointestinal tract as well as the low molecular weight. Centrally administered YL also exhibited anxiolytic-like activity at a dose of 0.1 nmol/mouse. This minimum effective dose after i.c.v. administration was two orders of magnitude smaller than that after i.p. administration (0.1 mg/kg equals to roughly 10 nmol/mouse), suggesting that its site of action might be the CNS. Further investigation will elucidate how dipeptide absorbed across the gastrointestinal tract and blood brain barrier (BBB) contributes to its anxiolytic-like activity.

We also investigated the mechanism underlying the anxiolytic-like activity of YL. This anxiolytic-like activity was blocked by antagonists for 5-HT_{1A}, D_1 and $GABA_A$ receptors; however, YL had no affinity for them. Thus we found that the anxiolytic-like activity of YL was mediated by the activation of 5-HT_{1A}, D_1 and $GABA_A$ receptors, but not by acting as an agonist of each receptor. The results of the structure-activity relationship study shown in Fig. 2 permit us to speculate that the unidentified YL receptor may bind to the N-terminus of YL and be activated, upstream of 5-HT_{1A}, D_1 and $GABA_A$ receptors. By pharmacological experiments using agonists and antagonists, we also determined that the order of activation was 5-HT_{1A}, D_1 and $GABA_A$ receptors. Thus, we hypothesized that the anxiolytic-like activity of YL was mediated as follows: YL → serotonin release → 5-HT_{1A} receptor → dopamine release → D_1 receptor → GABA release → $GABA_A$ receptor → anxiolytic-like activity. In addition, the possibility that YL exhibits anxiolytic-like activity via an enzyme inhibition-dependent mechanism in the CNS could not be ruled out.

It has been reported that a 5-HT_{1A} receptor agonist exhibits anxiolytic-like and antidepressant-like effects [16,17]. The 5-HT_{1A} receptor-knockout mice showed increased anxiety-like behavior [18,19]. 5-HT_{1A} receptors are localized not only in the serotonergic cell bodies of the raphe nuclei but also in non-serotonergic neurons in various brain regions, including the hippocampus, prefrontal cortex and ventral tegmental area (VTA) [20].

D_1 receptor agonist exhibited anxiolytic-like activity in previous and our studies, and mice lacking D_1 receptor showed anxiogenic behavior [1,6], suggesting that D_1 activation may decrease anxiety in mice. The mesocorticolimbic pathway with dopaminergic projection from the VTA to frontal cortex and/or nucleus accumbens is implicated in emotional and cognitive regulation, and the nigrostriatal pathway from the substantia nigra to the striatum is involved in motor function [21]. It was reported that systemic administration of 5-HT_{1A} agonist facilitated dopamine release in the frontal cortex or nucleus accumbems [20].

$GABA_A$ receptor is also well-known to be associated with anxiolytic-like behavior, and is a chloride channel composed of a pentameric heterooligomeric protein with binding sites for GABA, benzodiazepines (BZD), barbiturates, steroids, etc. The BZD site is located on the α subunit, while the GABA binding site is on the β-subunit. The activation of the $GABA_A$ receptor induced by BZD including diazepam reduces anxiety, whereas the γ2 subtype of $GABA_A$ receptor-knockout mice show increase anxiety [7,22,23].

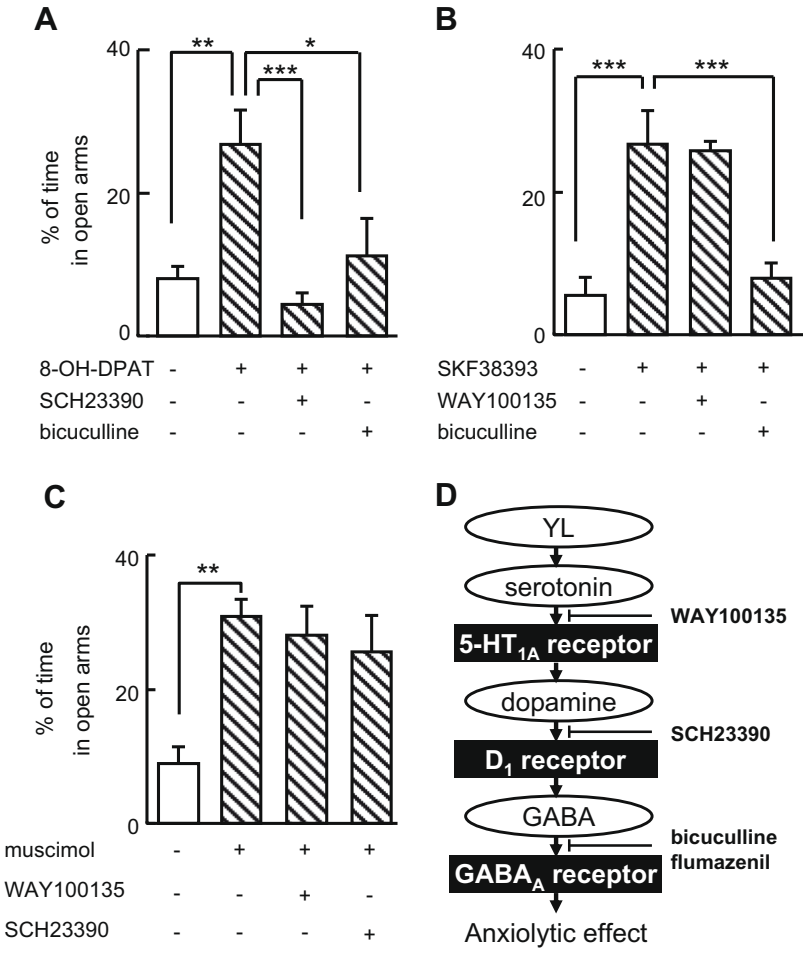

Fig. 5. Novel anxiolytic pathway via activation of 5-HT_{1A}, D_1 and $GABA_A$ receptors. The order of their activations was determined using 8-hydroxy (OH)-DPAT (A), SFK38393 (B) or muscimol (C), an agonist selective for 5-HT_{1A}, D_1 or $GABA_A$ receptor, respectively. The anxiolytic-like activity of 8-OH-DPAT (1 mg/kg, i.p.) was blocked by SCH23390 (30 μg/kg, i.p.) or bicuculline (5 mg/kg, i.p.), an antagonist for D_1 or $GABA_A$ receptor, respectively (A). The anxiolytic-like activity of SKF38393 (1 mg/kg) was inhibited by bicuculline (5 mg/kg, i.p.) but not by WAY100135 (10 mg/kg, i.p.), a 5-HT_{1A} receptor antagonist (B). The anxiolytic-like activity of muscimol (0.3 mg/kg, i.p.) was inhibited by neither WAY100135 (10 mg/kg, i.p.) nor SCH23390 (30 μg/kg, i.p., C). A scheme for the putative mechanism underlying the anxiolytic-like activity of YL (D). Values are the means ± S.E.M. (A, $n = 4–6$; B, $n = 4–5$; C, $n = 4–5$). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with each group.

Milco et al. reported that α-casozepine, a decapeptide derived from bovine α_{s1}-casein with affinity for the BZD site, exhibits anxiolytic-like activity after i.p. administration in rats. In contrast, YL did not have affinity for either BDZ or GABA sites of the $GABA_A$ receptor. The anxiolytic-like activity of YL was blocked by antagonists for both binding sites. Taken together, YL might show an anxiolytic-like effect after activating the GABA binding site, probably by stimulating presynaptic GABA release. Further investigation will elucidate where 5-HT_{1A}, D_1 and $GABA_A$ receptors in the CNS are activated after YL administration.

Among a number of bioactive peptides isolated from the enzymatic digest of food proteins, several short peptides exhibited anxiolytic-like activity after oral administration. We reported that soymorphin-5 (YPFVV) and rubiscolin-6 (YPLDLF), which are μ and δ opioid peptides derived from soy β-conglycinin and spinach Rubisco, respectively, had anxiolytic-like activities [1,3]. Rubiscolin-6 exhibits anxiolytic activity by activating σ_1 receptor, downstream of δ opioid receptor [3]; however, YL-induced anxiolytic-like activity was not blocked by antagonists for μ and δ opioid receptors and σ_1 receptor, naloxone, naltrindole and BMY14802, respectively (Supplementary Fig. S4A and B), suggesting that YL shows anxiolytic-like activity independently of these opioid systems. We have also reported that rubimetide (MRW) derived from Rubisco exhibited anxiolytic-like activities via activation of the prostaglandin (PG) D_2 system, which is a novel anxiolytic pathway [4,8]. The anxiolytic-like activity of YL was not significantly attenuated by a cyclooxygenase inhibitor, indomethacin (Supplementary Fig. S4C), suggesting that YL might be independent of the PG D_2 system.

YL sequences are present in the primary structure of many endogenous and exogenous proteins, including serum albumin and natural food proteins such as milk and soy beans. Tripeptides having a YL sequence in the N-termini maintain anxiolytic-like activities. In addition, YLYEIAR, a serum albumin-derived heptapeptide having a YL sequence in the N-terminus also exhibited anxiolytic-like activity (unpublished observation). These results might not rule out the possibility that food protein-derived peptides having a YL sequence after digestion by enzymes present in the gastrointestinal tract potentially contribute to anxiolytic-like activity in the post-prandial state.

In conclusion, YL had anxiolytic-like activity in the elevated plus-maze test after i.p. (0.1 mg/kg) or oral (0.3 mg/kg) administration in mice, and this effect was blocked by antagonists for 5-HT_{1A}, D_1 and $GABA_A$ receptors; however, YL had no affinity for them. We determined the order of activation of 5-HT_{1A}, D_1 and $GABA_A$ receptors in anxiolytic-like activity using agonists and antagonists for them. The anxiolytic-like activity of YL was mediated by the activation of 5-HT_{1A} and dopamine D_1 receptor followed by $GABA_A$ receptor.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.febslet.2009.12.008.

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