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Straub tail reaction in mice treated with σ_1 receptor antagonist in combination with methamphetamine

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Abstract

Straub tail reaction (STR) was observed in male ddY mice after simultaneous administration with BMY 14802 (a non-specific σ receptor antagonist) and methamphetamine (METH). The intensity and duration of STR depended on the dose of BMY 14802. The tail reaction was inhibited completely by (+)-SKF 10,047 (a putative σ_1 receptor agonist) and partially by PB 28 (a putative σ_2 receptor agonist). The STR was mimicked in mice treated with BD 1047 (a putative σ_1 receptor antagonist), but not SM-21, a putative σ_2 receptor antagonist, in combination with METH. STR evoked with BD 1047 plus METH was inhibited by (+)-SKF 10,047. STR induced by BMY 14802 and METH was abolished by naloxone (a relatively non-selective opioid receptor antagonist) or U-50,488H (a selective κ -agonist), suggesting that the STR may be mediated by activation of opioid receptor system.

Keywords

Methamphetamine; σ ligand; Straub tail reaction; Opioid receptor system

1. Introduction

Straub tail reaction (STR) is a dorsiflexion of the tail that is often almost vertical to the orientation of the body or curling back over the animal, even curling over in a “pig-like” circular fashion produced by contraction of the sacrococcygeus muscle (Bilbey et al, 1960). This phenomenon was first described as a response to opiates in mice (Straub, 1911), and is thought to be mediated by activation of the opioid receptor system because opioid receptor antagonists such as naloxone, nalorphine and β -funaltrexamine block the phenomenon (Aceto et al, 1969; Nath et al., 1994; Zarrindast et al, 2001) although κ opioid antagonists have also been shown to reduce morphine-induced STR (Narita et al, 1993). Serotonergic, noradrenergic and dopaminergic mechanisms have also been implicated in opiate-induced STR (Kameyama et al, 1978, 1979; Blumberg and Slovak, 1982; Hasegawa et al., 1990; Zarrindast et al, 2001, 2002). Amphetamine can potentiate morphine-induced STR and this effect is mediated by noradrenergic mechanisms (Blumberg and Slovak, 1982). However,

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STR was also part of the “serotonin syndrome” produced by serotonergic agonists (Trulson et al, 1976a, b), including selective 5-HT_{1A} receptor agonists (Blanchard et al, 1997) and can also be produced by dopaminergic agonists (Hasegawa et al, 1990; Zarrindast et al, 1993), α_2 noradrenergic agonists (Pranzatelli et al, 1987), and nicotinic acetylcholine receptor agonists (Spande et al., 1992; Fonck et al, 2003). The mechanisms of non-opioid agents that induce STR have been suggested to be both dependent and independent of opioid receptor systems.

Previously, we examined the effects of σ receptor ligands on methamphetamine (METH)-induced stereotypy in mice (Kitanaka et al, 2009). In this series of the experiments, we observed that the tail was dorsiflexed over the backs of mice treated with σ receptor antagonists in combination with METH. In the present study, we investigated the characteristics of the STR induced by σ receptor antagonist in combination with METH in mice, compared to the STR induced by morphine in terms of a time-course, to determine whether our previous observation of STR may indicate that the combination of these drugs may be affecting opioidergic mechanisms.

2. Results

Table 1 shows the experimental treatment groups described below.

2.1. Morphine-induced STR

Mice were treated with morphine, morphine plus the relatively non-selective opioid antagonist naloxone (naloxone/morphine), or morphine plus the selective κ opioid agonist U-50,488H (U-50,488/morphine). Fig. 1 shows the time course of STR observed in mice immediately after a single injection (i.p.) of morphine (30 mg/kg). There was an increase in the STR in the mice after morphine challenge, beginning at 5 min post-injection, reaching a maximum at 20 min post-injection, and continuing unabated for the duration of the test session. Treatment of mice with naloxone (15 mg/kg) or U-50,488H (8 mg/kg) almost completely attenuated the STR induced by morphine. A repeated-measures ANOVA (treatment x time) applied to the data represented in Fig. 1 yielded significant main effects of treatment ($F(2, 21) = 49.2, P < 0.0001$) and time ($F(12, 273) = 13.5, P < 0.0001$). This analysis also yielded a significant treatment x time interaction ($F(24, 273) = 8.3, P < 0.0001$). *Post-hoc* pair-wise comparisons (Bonferroni/Dunn test) showed significant differences of time course between morphine and naloxone/morphine and between morphine and U-50,488/morphine ($P < 0.05$) at all time points after 0 min.

2.2. BMY 14802/METH-induced STR: dose-response for BMY 14802

Mice were treated with one of three different doses of the non-selective σ receptor antagonist BMY 14802 (1, 5, or 10 mg/kg, i.p.) in combination with 10 mg/kg of METH (i.p.). Fig. 2 shows the time course of STR observed in mice immediately after a single injection of METH 30 min after BMY 14802 pretreatment. Combined treatment with METH and differing doses of BMY 14802 produced a BMY 14802 dose-dependent increase in STR, beginning at 15 min post-injection, reaching a maximum at 20 min post-injection in the mice pretreated with 10 mg/kg of BMY 14802. There was negligible change in mice treated with METH and the lowest dose of BMY 14802, but an obvious, but transient increase, in STR in mice after METH challenge combined with the 5 mg/kg BMY 14802. Combined treatment with METH and 10 mg/kg BMY 14802 produced a prolonged elevation in STR that lasted for the majority of the 1 h assessment period. A repeated-measures ANOVA (BMY 14802 dose x time) applied to the data represented in Fig. 2 yielded significant main effects of treatment ($F(2, 21) = 106.1, P < 0.0001$) and time ($F(12, 273) = 18.2, P < 0.0001$). This analysis also yielded a significant treatment x time

interaction ($F(24, 273) = 18.0, P < 0.0001$). *Post-hoc* pair-wise comparisons showed significant differences of time course between BMY 14802 (10 mg/kg)/METH and BMY 14802 (1 mg/kg)/METH, and between BMY 14802 (10 mg/kg)/METH and BMY 14802 (5 mg/kg)/METH ($P < 0.05$), treatment groups for the periods between 20 and 50 min post-injection. We also assessed the effects of a lower METH dose. Hyperlocomotion without STR was observed when mice were administered with BMY 14802 (1, 5 and 10 mg/kg) in combination with 5 mg/kg METH (data not shown). When mice were administered BMY 14802 (1, 5 and 10 mg/kg) in combination with 20 mg/kg METH, the mice showed stereotypical behavior including biting and/or self-injurious behavior (data not shown), suggesting that the dose of 10 mg/kg may be optimal for expression of STR in combination with BMY 14802.

2.3. BMY 14802/METH-induced STR: effects of σ receptor agonists and opioid agents

In the previous experiment (Fig. 2), administration of BMY 14802 in combination with METH induced a long-lasting STR. The effects of the relatively non-selective opioid antagonist naloxone, the selective κ opioid receptor agonist U-50,488H and σ agonists (SKF 10,047 and PB 28, putative selective σ_1 and σ_2 receptor agonists, respectively) on the STR induced by BMY 14802 plus METH were investigated. Mice were randomly divided into four groups and given SKF 10,047 (4 mg/kg, i.p.), PB 28 (1 mg/kg, i.v.), naloxone (15 mg/kg, i.p.), or U-50,488H (8 mg/kg, s.c.) treatment in combination with BMY 14802 plus METH as in the previous experiments. The time course for STR induced by BMY 14802 plus METH shown in Fig. 3 is very similar to the time course observed in the previous experiment (Fig. 2). As shown in Fig. 3, STR induced by BMY 14802 plus METH was almost completely blocked by treatment with SKF 10,047, naloxone, or U-50,488H. The STR induced by BMY 14802 plus METH was also substantially attenuated by treatment with PB 28, although there was an initial significant increase in STR in this group. A repeated-measures ANOVA (treatment $\times$ time) applied to the data represented in Fig. 3 yielded significant main effects of treatment ($F(4, 35) = 36.7, P < 0.0001$) and time ($F(12, 455) = 18.1, P < 0.0001$). This analysis also yielded a significant treatment $\times$ time interaction ($F(48, 455) = 8.2, P < 0.0001$). *Post-hoc* pair-wise comparisons showed significant differences of time-course between BMY 14802/METH and all other groups for most time-points between 20 and 50 min post-injection ($P < 0.05$; see Fig. 3).

2.4. STR induced by selective antagonists for σ receptor subtypes

Contribution of σ receptor subtypes to STR observed in Figs 2 and 3 was investigated using the σ receptor antagonists BD 1047 and SM-21, putative σ_1 and σ_2 receptor antagonists, respectively. Mice were randomly divided into four groups: BD 1047 (10 mg/kg, i.p.), SM-21 (1 mg/kg, i.p.), BD 1047 plus (+)-SKF 10,047 (4 mg/kg, i.p.), or BD 1047 plus PB 28 (1 mg/kg, i.v.), in combination with METH. Thus, the four treatment groups were BD 1047/METH, SM-21/METH, BD 1047/SKF 10,047/METH and BD 1047/PB 28/METH. As shown in Fig. 4, BD 1047 induced a significant and long-lasting increase in the STR in combination with 10 mg/kg of METH (BD 1047/METH). The STR was blocked partially by (+)-SKF 10,047 (BD 1047/SKF 10,047/METH), and to lesser extent, by PB 28 (BD 1047/PB 28/METH). In each case there was still a transient increase in STR that was of much shorter duration than without antagonist treatment, although the magnitude of the response was the same. By contrast, SM-21 had little effect on STR in combination with METH (SM-21/METH), except for a transient, non-significant increase observed at the 10 min time-point. A repeated-measures ANOVA (treatment $\times$ time) applied to the data represented in Fig. 4 yielded significant main effects of treatment ($F(3, 20) = 30.9, P < 0.0001$) and time ($F(12, 260) = 39.7, P < 0.0001$). This analysis also yielded a significant treatment $\times$ time interaction ($F(36, 260) = 13.5, P < 0.0001$). *Post-hoc* pair-wise comparisons showed significant differences between BD 1047/METH and all other groups from 25 to 45 min

post-injection, and additionally from BD 1047/SKF 10,047/METH and SM-21/METH between 15 and 25 min post-injection ($P < 0.05$). Significant differences were also observed between BD 1047/PB 28/METH and BD 1047/SKF 10,047/METH and between BD 1047/PB 28/METH and SM-21/METH ($P < 0.05$) between 15 and 20 min post-injection.

3. Discussion

Mice treated with a single injection of morphine (30 mg/kg) showed a significant STR, which was blocked by naloxone, a relatively non-selective opioid receptor antagonist or U-50,488H, a selective κ -agonist (Fig. 1). These observations are consistent with the previously published reports describing STR (Aceto et al., 1969; Narita et al., 1993; Nath et al., 1994). As shown in Fig. 1, the STR induced by morphine reached a plateau level at a time point of 20 min after morphine challenge while the STR was completely blocked by naloxone or U-50,488H up to 60 min after morphine challenge. Using this method, we investigated the ability of a non-selective σ receptor antagonist to produce STR when administered in combination with METH compared to the STR induced by morphine in terms of a time-course, to determine whether our previous observation of STR may indicate that the combination of these drugs may be affecting opioidergic mechanisms. As shown in Fig. 2, the intensity and duration of STR depended on the dose of BMY 14802, although preliminary experiments indicated that this effect, or the observation of other METH-induced behaviors (e.g. locomotion and stereotypy), also depended on the concentration of METH. The dose of METH used in the present study was optimal for producing STR as opposed to the other behavioral effects of METH. Maximal intensity and duration of STR were observed by treatment of mice with 10 mg/kg BMY 14802 in combination with 10 mg/kg METH (Fig. 2). The STR induced by BMY 14802 plus METH was almost completely blocked by naloxone as well as U-50,488H (Fig. 3), suggesting that the STR was elicited via an opioid-dependent mechanism, similar to morphine-induced STR (Aceto et al, 1969; Narita et al., 1993; Nath et al., 1994). Nath et al. (1994) suggested that both morphine induced analgesia and STR are induced by morphine actions at the putative μ_1 and μ_2 receptor subtypes, respectively. It must be noted that there is a single μ opioid receptor gene (Wang et al, 1993) and that these putative “subtypes” of the μ opioid receptor are based upon pharmacological considerations (Ling et al., 1989), the basis of which may be alternative splicing of the μ opioid receptor gene (Rossi et al, 1995). Synergistic effects of σ receptor antagonists and morphine on analgesia have also been reported (Chien and Pasternak, 1995). In the present study, we did not find synergistic effects of BMY 14802 and METH for analgesia in the hot-plate test (data not shown). This suggests that, at least in part, the synergistic effects of σ receptor antagonists with morphine (Chien and Pasternak, 1995) and with METH (Fig. 2) have a somewhat different basis, perhaps the interactions with METH involving a specific μ opioid receptor subtype, as previously suggested. Alternatively, it might also be possible that the effects of non-selective μ receptor antagonists on analgesia and STR involve different σ receptor subtypes. Under the experimental conditions used in the present study, the duration of the activation of the opioid receptor system by the combination of a σ_1 receptor antagonist and METH is a little less than 1 h (Figs. 2 and 4) whereas of the STR induced by morphine lasted longer than the 1 h observation period (Fig. 1). This may be due to a transient release of endogenous opioids and/or a relatively higher rate of metabolism for the σ_1 receptor antagonist and/or METH compared to morphine.

There are two proposed σ receptor subtypes, designated as σ_1 and σ_2 (for reviews see Matsumoto et al, 2003; Guitart et al, 2004). It is likely that BMY 14802 (a non-selective σ receptor antagonist) induces STR via its binding predominantly to the σ_1 receptor subtype because the STR was completely blocked by SKF 10,047, a selective σ_1 receptor agonist, but was only partially attenuated partially by PB 28, a selective σ_2 receptor agonist (Fig. 3).

This analysis is further supported by the data shown in Fig. 4. BD 1047, a selective σ_1 receptor antagonist, but not SM-21, a selective σ_2 receptor antagonist, induced STR when administered to mice in combination with METH. The STR was also blocked by SKF 10,047 but not PB 28, suggesting again that the STR is mediated by the σ_1 receptor subtype.

The molecular mechanisms underlying the expression of STR have yet to be completely elucidated. As discussed previously, various monoaminergic mechanisms have been suggested to have roles in opiate-induced STR (Kameyama et al, 1978; Gupta et al, 1988; Zarrindast et al, 2002) or to independently induce STR (Trulson et al, 1976a, b; Pranzatelli et al, 1987; Hasegawa et al, 1990; Zarrindast et al, 1993; Blanchard et al, 1997). For instance, pretreatment of mice with phenoxybenzamine or propranolol (α - and β -adrenergic receptor antagonists, respectively) significantly inhibits, while pretreatment with METH significantly enhances, morphine-induced STR, suggesting an involvement of adrenergic neurotransmission in morphine-induced STR (Kameyama et al, 1978). Clonidine can induce STR (Pranzatelli et al, 1987) and spontaneous STR is observed in norepinephrine transporter knockout (NET KO) mice (observation noted in Hall et al, 2011). Indeed those observations were made during a series of studies investigating nociception in NET KO mice which had profound hypoalgesia (Hall et al, 2011). In the present study, METH actions may also have been mediated by its ability to potentiate adrenergic neurotransmission by inhibition of NET (Sora et al, 2009). The mechanism underlying the effects of the intracellular σ_1 receptor is still largely unknown (Su and Hayashi, 2003), although its putative role in receptor trafficking via effects on lipid rafts (Genedani et al., 2010) may suggest a mechanism for enhancing METH effects.

The present results may indicate that the novel intracellular signal transduction mechanism elicited by σ receptor ligands may affect the behavioral actions of both METH and morphine. It remains to be seen whether the same mechanisms are involved in each of these effects, although certainly some data suggests that this may be the case. This furthermore suggests that drugs that modulate σ receptors may be useful in modulating other effects of drugs of abuse, such as METH and morphine, a possibility that will require further investigation.

4. Materials and Methods

4.1. Subjects

Male ddY mice (10 weeks old; Japan SLC, Shizuoka, Japan) were housed in groups of eight (cage size, 37 × 22 × 15 cm; with fresh wood chips) in a temperature-(22 ± 2°C) and humidity- (50 ± 10%) controlled environment under a 12 h light/dark cycle (lights on at 07:00) with food and water available *ad libitum*, except during testing. Observation of STR was made by trained observers. Animal handling and care were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* (7th edition, Institute of Laboratory Animal Resources-National Research Council, National Academy Press, 1996), and all experiments were reviewed and approved by the Institutional Animal Research Committee of Hyogo College of Medicine. The mice were only used once ($n = 104$, 11-12 weeks old, 37-53 g) after at least one-week habituation in the facility.

4.2. Reagents

METH HCl was purchased from Dainippon Sumitomo Pharma Co., Ltd. (Osaka, Japan). Morphine hydrochloride was purchased from Takeda Chemical Industries (Osaka, Japan). BMY 14802 hydrochloride (α -(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinebutanol hydrochloride, a non-specific σ receptor antagonist), BD 1047 dihydrobromide (*N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(dimethylamino)ethylamine

dihydrobromide, a putative σ_1 receptor antagonist), SM-21 maleate (($\pm$)-tropanyl 2-(4-chlorophenoxy)butanoate maleate, a putative σ_2 receptor antagonist), (+)-SKF 10,047 hydrochloride ([2*S*-(2 α ,6 α ,11 *R*)]-1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazocin-8-ol hydrochloride, a putative σ_1 receptor agonist), and PB 28 dihydrochloride (1-cyclohexyl-4-[3-(1,2,3,4-tetrahydro-5-methoxy-1-naphthalen-1-yl)-*n*-propyl]piperazine dihydrochloride, a putative σ_2 receptor agonist) were purchased from Tocris Cookson, Inc. (Ellisville, MO, USA). Naloxone hydrochloride dihydrate (a relatively non-selective opioid receptor antagonist) and U-50,488H ((-)-*trans*-(1*S*,2*S*)-U-50,488 hydrochloride hydrate, a highly selective κ -opioid receptor agonist) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Doses of drugs refer to the weight of the salt. All reagents were dissolved in sterile saline. Drug solutions were prepared in such a way that the necessary dose could be injected in a volume of 0.1 ml/10 g of body weight by an i.p. route (METH, morphine, naloxone, BMY 14802, BD 1047, SM-21, and (+)-SKF 10,047), in a volume of 0.1 ml/10 g of body weight by an s.c. route (U-50,488H) or in a volume of 0.025 ml/10 g of body weight by i.v. tail injection (PB 28). The doses of the drugs and the routes of injection were chosen based on the literature (Narita et al, 1993; Kamei et al, 1994; Kassiou et al., 2005; Kitanaka et al, 2009).

4.3. Treatment protocol

4.3.1. Morphine-induced STR—Mice ($n = 24$) were weighed and randomly divided into three groups ($n = 8$ per group): morphine, naloxone/morphine and U-50,488H/morphine. Morphine subjects were treated with morphine alone (30 mg/kg, i.p.). Naloxone/morphine subjects were treated with naloxone (15 mg/kg, i.p.) and immediately injected with morphine (30 mg/kg, i.p.). U-50,488H/morphine subjects were treated with U-50,488H (8 mg/kg, s.c.) 10 min prior to morphine treatment (30 mg/kg, i.p.). This period of pretreatment for U-50,488H was chosen based on the literature (e.g. Narita et al, 1993). After treatment with morphine all mice were immediately placed in the testing chamber to assess STR for 1 h as described below (see 4.4. Rating of STR).

4.3.2. BMY 14802/METH-induced STR: dose-response for BMY 14802—Mice ($n = 24$) were weighed, randomly divided into three groups ($n = 8$ per group), and treated with 10 mg/kg of METH (i.p.) 30 min after an injection of BMY 14802 (1, 5, or 10 mg/kg, i.p.). After the METH challenge injection, all mice were placed in the testing chamber for measurement of STR.

4.3.3. BMY 14802/METH-induced STR: effects of σ receptor agonists and opioids—Mice ($n = 40$) were weighed and randomly divided into five groups ($n = 8$ per group): METH/BMY 14802, METH/BMY 14802/naloxone, METH/BMY 14802/SKF 10,047, METH/BMY 14802/PB 28, METH/BMY 14802, and METH/BMY 14802/U-50,488H. All subjects were treated with 10 mg/kg of METH 30 min after injection with 10 mg/kg of BMY 14802. The subjects assigned to the group that was treated with (+)-SKF 10,047 plus BMY 14802/METH were pretreated with 4 mg/kg (+)-SKF 10,047 (i.p.). The group treated with PB 28 received 1 mg/kg PB 28 (i.v.) in combination with BMY 14802 30 min prior to METH challenge. The subjects assigned to a group that was treated with naloxone plus BMY 14802/METH were given with 15 mg/kg naloxone (i.p.). The subjects assigned to the group that was treated with U-50,488H plus BMY 14802/METH were pretreated with U-50,488H (8 mg/kg, s.c.) 10 min prior to METH challenge (i.e. 20 min after BMY 14802 pretreatment). After the METH challenge injection, all mice were placed in the testing chamber for measurement of STR.

4.3.4. STR induced by selective antagonists for a receptor subtypes—Mice ($n = 24$) were weighed and randomly divided into four groups ($n = 6$ per group): BD 1047/

METH, SM-21/METH, SKF 10,047/BD 1047/METH, and PB 28/BD 1047/METH. All subjects were treated with 10 mg/kg of METH. BD 1047/METH subjects were treated with METH 30 min after 10 mg/kg of BD 1047 (i.p.). SM-21/METH subjects received METH 30 min after 1 mg/kg of SM-21 (i.p.). The SKF 10,047/BD 1047/METH and PB 28/BD 1047/METH groups were injected with the agonists selective for σ receptor subtypes (+)-SKF 10,047 or PB 28 and injection with METH and BD 1047 as in the previous experiment. After the METH challenge injection, all mice were placed in the testing chamber for measurement of STR.

4.4. Rating of STR

The animals in the transparent acrylic testing chamber (30 × 30 × 35 cm) were observed for STR for 1 h immediately after the final drug administration by observers unaware of the treatments. The positive tail response was considered as a persistent elevation of the tail at an angle more than 45° (Aceto et al., 1969; Nath et al., 1994). Experiments were conducted under sound-attenuated conditions to minimize the effects of noise on the Straub tail response. The behavior was broken down into 30-s bins, and the tail reaction was recorded for each bin when it was a predominant behavior. The cumulative number of bins within every 5-min period was shown as a time course (maximal value = 10).

4.5. Statistics

Data are presented as mean ± the standard error of the mean (SEM). Statistical analysis was performed using mixed factor analysis of variance (ANOVA), with or without repeated measures as appropriate, followed by Bonferroni-Dunn *post hoc* comparisons individual means for significant factors (Statview 5.0 for Apple Macintosh, SAS Institute, Inc., Cary, NC, USA). Statistical significance was set at $P < 0.05$.

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Fig. 1.

Straub tail reaction in mice after morphine challenge. The positive Straub tail response was considered as a persistent elevation of the tail at an angle more than 45°. Values are shown as the mean $\pm$ the standard error of the mean ($n = 8$ for each group). * $P < 0.05$, significant difference between morphine and naloxone/morphine and between morphine and U-50,488/morphine (Bonferroni/Dunn test).

Fig. 2.

Straub tail reaction in mice after METH in combination with doses of BMY 14802. Values are shown as the mean $\pm$ the standard error of the mean ($n = 8$ for each group). * $P < 0.05$, significant difference between BMY 14802 (10 mg/kg)/METH and the other two dose conditions (Bonferroni/Dunn test).

Fig. 3.

Straub tail reaction in mice after BMY14802/METH in combination with putative selective σ receptor agonists ((+)-SKF 10,047 and PB 28) or opioid agents (naloxone and U-50,488H). Values are shown as the mean $\pm$ the standard error of the means ($n = 8$ for each group). * $P < 0.05$, significant difference between BMY 14802/METH and all other groups (Bonferroni/Dunn test). † $P < 0.05$, significant difference between PB 28/BMY 14802/METH and SKF 10,047/BMY 14802/METH, between PB 28/BMY 14802/METH and naloxone/BMY 14802/METH, and between PB 28/BMY 14802/METH and U-50,488H/BMY 14802/METH (Bonferroni/Dunn test).

Fig. 4.

Straub tail reaction induced by putative selective antagonists for σ receptor subtypes. Values are shown as the mean $\pm$ the standard error of the means ($n = 6$ for each group). * $P < 0.05$, significant difference between BD 1047/METH and all other groups. † $P < 0.05$, significant difference between BD 1047/PB 28/METH and BD 1047/SKF 10,047/METH and between BD 1047/PB 28/METH and SM-21/METH.

Table 1**Treatment protocol**

shows the experimental treatment groups described below.

Methods section	Pretreatment (pretreatment period)	Challenge	<i>n</i>
4.3.1	–	Morphine	8
	–	Naloxone/Morphine	8
	U-50,488H (10 min)	Morphine	8
4.3.2	1 mg/kg BMY 14802 (30 min)	METH	8
	5 mg/kg BMY 14802 (30 min)	METH	8
	10 mg/kg BMY 14802 (30 min)	METH	8 ^a
4.3.3	BMY 14802 (30 min)	METH	8 ^a
	(+)-SKF 10,047/BMY 14802 (30 min)	METH	8
	PB 28/BMY 14802 (30 min)	METH	8
	BMY 14802 (30 min)	Naloxone/METH	8
	BMY 14802 (30 min)/U-50,488H (10 min)	METH	8
4.3.4	BD 1047 (30 min)	METH	6
	SM-21 (30 min)	METH	6
	(+)-SKF 10,047/BD 1047 (30 min)	METH	6
	PB 28/BD 1047 (30 min)	METH	6

Doses and the routes of injection of the drugs were described in each section of the Experimental Procedures.

^a Identical test group.