Available online at www.sciencedirect.com

SCIENCE DIRECT

Brain Research 1057 (2005) 72 – 80

BRAIN RESEARCH

www.elsevier.com/locate/brainres

Research Report

Improvement of memory impairment by (+)- and (−)-pentazocine via sigma, but not kappa opioid receptors

Masayuki Hiramatsu[a,b,*], Takashi Hoshino[b]

[a]Laboratory of Neuropsychopharmacology, Graduate School of Environmental and Human Sciences, Tenpaku-ku, Nagoya 468-8503, Japan
[b]Department of Chemical Pharmacology, Faculty of Pharmaceutical Sciences, Meijo University, Tenpaku-ku, Nagoya 468-8503, Japan

Accepted 19 July 2005
Available online 26 August 2005

Abstract

(±)-Pentazocine is widely used clinically to treat mild to moderate pain as a racemic compound. Although it is known that (−)-pentazocine acts as a kappa opioid receptor agonist to exhibit analgesic actions and (+)-pentazocine acts as a sigma receptor agonist without analgesic effects, their combined effect on memory has not been investigated in detail. In this study, the effect of (+)- and/or (−)-pentazocine on scopolamine-induced memory impairment in mice was investigated using spontaneous alternation performance in a Y-maze. (+)-Pentazocine (0.35 μmol/kg, s.c.) administered 30 min before behavioral testing significantly improved the impairment of spontaneous alternation induced by scopolamine. A higher dose of (−)-pentazocine (3.50 μmol/kg, s.c.) also reversed the scopolamine-induced impairment of alternation performance. Interestingly, the ameliorating effects of not only (+)-pentazocine, but also (−)-pentazocine were antagonized by a selective sigma receptor antagonist, *N*,*N*-dipropyl-2-[4-methoxy-3-(2-phenylenoxy)-phenyl]-ethylamine monohydrochloride (NE-100) (2.6 μmol/kg, i.p.). However, those effects were not antagonized by a selective kappa opioid receptor antagonist, nor-binaltorphimine (4.9 nmol/mouse, i.c.v.). Coadministration of (+)- and (−)-pentazocine (0.35 or 3.50 μmol/kg each) did not have any additive or antagonizing effects on the percent alternation. An antinociceptive effect was observed only with (−)-pentazocine (3.50 μmol/kg, s.c.), and was antagonized by nor-binaltorphimine (4.9 nmol/mouse, i.c.v.), but not by NE-100 (2.6 μmol/kg, i.p.). These results suggest that although the analgesic effect of pentazocine was mediated via kappa opioid receptors, the ameliorating effect on scopolamine-induced impairment of spontaneous alternation was mediated via sigma receptors, not via kappa opioid receptors.

Theme: Neural basis of behavior
Topic: Learning and memory: pharmacology

Keywords: (−)-Pentazocine; Sigma receptor; Kappa opioid receptor; Spontaneous alternation; Memory; Antinociceptive effect

1. Introduction

Previously, we reported that kappa opioid receptor agonists, such as *trans*-(±)-3,4-dichloro-*N*-methyl-*N*-(2-[1-pyrrolidinyl] cyclohexyl) benzeneacetamide methanesulfonate (U-50,488H) and dynorphin A (1–13), improved learning and memory impairment using several amnesia models in a nor-binaltorphimine (nor-BNI)-dependent manner in mice and rats [9,12–14,17]. It is well recognized that the analgesic effects of (±)-pentazocine are due to agonistic actions at kappa1 opioid receptors [29]. Pentazocine is widely used clinically as an analgesic, but only a racemate is available [1,29]. Higher doses of pentazocine elicit dysphoric and psychotomimetic effects similar to those of nalorphine, but the mechanisms responsible for these side effects are not known [35]. All the analgesic actions reside with the (−)-isomer which is selective for kappa opioid receptors [3]. On the other hand, the (+)-isomer has little affinity for opioid receptors [29]. Quirion et al. [28] reported that the (+)-isomer was relatively selective of sigma1 ligand, and activation of

* Corresponding author. Laboratory of Neuropsychopharmacology, Graduate School of Environmental and Human Sciences, and Department of Chemical Pharmacology, Faculty of Pharmaceutical Sciences, Meijo University, Tenpaku-ku, Nagoya 468-8503, Japan. Fax: +81 52 834 8780.
E-mail address: mhiramt@ccmfs.meijo-u.ac.jp (M. Hiramatsu).

0006-8993/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2005.07.028

sigma receptors by (±)-*N*-allylnormetazocine [(±)-SKF-10,047], a prototype sigma receptor agonist, caused psychotomimetic effects [10,19,21]. Interestingly, sigma receptor agonists such as (+)-pentazocine and 1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl) piperazine dihydrochloride (SA4503), ameliorated the impairment of learning and memory in mice [25,26] and this effect was antagonized by a selective sigma receptor antagonist, *N*,*N*-dipropyl-2-[4-methoxy-3-(2-phenylenoxy)-phenyl]-ethylamine monohydrochloride (NE-100) [25]. (±)-SKF-10,047 enhanced stimulation-evoked acetylcholine (ACh) release in guinea pig cerebral slices [32]. Moreover, it was reported that the sigma receptor agonists, (+)-SKF10,047 and (+)-pentazocine, increased extracellular ACh levels in the rat frontal cortex [22,23] and hippocampus [24]. The activation of the central cholinergic system by (+)-SKF10,047 was antagonized by haloperidol at a dose range compatible with its sigma1 receptor antagonistic action [23,24]. Therefore, sigma receptor agonists may be effective in improving learning and memory impairment involving the cholinergic system.

Pasternak and colleagues reported that a tonically active anti-opioid sigma receptor system markedly influenced the sensitivity of mice toward opioid analgesics, particularly kappa opioid drugs [2–4]. When gene expression was inhibited by the sigma1 receptor antisense, the analgesic activities of both the kappa1 and kappa3 opioid receptor agonists, respectively, U-50,488H and naloxone benzoylhydrazone, were enhanced [20]. Further, a putative sigma receptor antagonist, haloperidol, enhanced kappa1, kappa3, and delta analgesia more markedly than morphine [3].

These results suggest interaction between the kappa opioid receptor and sigma receptor in the central nervous system in analgesic functions that may also be relevant for memory functions. In this study, the improvement of short-term memory by (+)- and (−)-pentazocine following scopolamine-induced impairment in mice was investigated using spontaneous alternation behavior in a Y-maze. This behavioral test was used as a first-screening test for the anti-amnesic effects of pentazocine, since it is very sensitive for the anti-amnesic effect and does not constrain the animals. We have compiled several data sets using this method accompanied by a passive avoidance test [11–13,17]. Furthermore, we re-examined the combined influence of these isomers on analgesic effects using an acetic acid-induced writhing test in mice.

2. Materials and methods

2.1. Animals

Seven-week-old male ddY mice (Japan SLC, Japan) were kept in a controlled environment with a 12-h light/12-h dark cycle and given food and tap water ad libitum. Experimental protocols concerning the use of laboratory animals were approved by the committee of Meijo University and were performed in accordance with the guidelines of the Japanese Pharmacological Society (Folia Pharmacol. Japon, 1992, 99: 35 A) and the interministerial decree of May 25th, 1987 (The Ministry of Education).

2.2. Drugs

The following drugs were used: (+)- and (−)-pentazocine (Santen Pharmaceuticals, Inc., Osaka, Japan); *N*,*N*-dipropyl-2-[4-methoxy-3-(2-phenylenoxy)-phenyl]-ethylamine mono-hydrochloride (NE-100, Taisho Pharmaceuticals, Inc., Tokyo, Japan); nor-binaltorphimine (nor-BNI, Research Biochemicals, Inc., Natrick, MA); and scopolamine hydrobromide (scopolamine, Tokyo Chemical Industry, Co., Ltd., Tokyo, Japan). Doses of all drugs were expressed as those of the bases. Drugs were dissolved in isotonic saline solution (Otsuka Pharmaceuticals, Inc., Tokyo, Japan).

2.3. Schedule for drug injection

Nor-BNI (4.9 nmol/mouse) was administered 30 min before the Y-maze session and the period of acetic acid-induced writhing test. Administration was made unilaterally into the lateral ventricle (i.c.v.) of the mouse brain according to the methods of Haley and McCormick [7] in a volume of 5 μl/mouse under brief ether anesthesia. (+)-Pentazocine (0.35, 1.05, 3.5, and 10.5 μmol/kg), (−)-pentazocine (0.35, 1.05, 3.5, and 10.5 μmol/kg), and/or scopolamine (1.65 μmol/kg) were administered subcutaneously (s.c.) 30 min before and NE-100 (2.6 μmol/kg) was administered intraperitoneally (i.p.) 30 min before the Y-maze session at a volume of 0.1 ml/10 g body weight. Control mice received saline s.c. or i.p. and/or i.c.v. at the same volume. The doses and sites of antagonists, nor-BNI and NE-100 were chosen according to our previous reports (e.g., [12,15]).

2.4. Acetic acid-induced writhing test

The writhing test was conducted at 30 min after s.c. injection of (+)- or (−)-pentazocine. Nor-BNI (4.9 nmol/mouse, i.c.v.) and NE-100 (2.6 μmol/kg, i.p.) were administered immediately before pentazocine injection. Twenty minutes after the injection of pentazocine, mice were treated with a 0.7% acetic acid solution i.p. at a volume of 0.1 ml/10 g body weight and placed in individual Plexiglas boxes for observation, and then 10 min later, the number of writhing responses was recorded for a 10-min period.

2.5. Spontaneous alternation behavior

Immediate working memory performance was assessed by recording spontaneous alternation behavior during a single session in a Y-maze [12,17] with minor modification from the original report in rats [30]. Although this paradigm includes exploratory, locomotor, motivational and systematic behaviors, and selectivity involving memory and especially learning processes are weak, we used this as a first-intent test, since it remains somehow pharmacologically predictive and not