Pharmacological Reports 67 (2015) 160–165

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Original research article

Antidepressant-like activity of a new piperazine derivative of xanthone in the forced swim test in mice: The involvement of serotonergic system

Karolina Pytka [a,*], Anna Rapacz [a], Małgorzata Zygmunt [a], Adrian Olczyk [b], Anna Waszkielewicz [c], Jacek Sapa [a], Barbara Filipek [a]

[a] Department of Pharmacodynamics, Faculty of Pharmacy, Jagiellonian University Medical College, Kraków, Poland
[b] Institute of Automatic Control, Silesian University of Technology, Gliwice, Poland
[c] Department of Bioorganic Chemistry, Chair of Organic Chemistry, Faculty of Pharmacy, Jagiellonian University Medical College, Kraków, Poland

ARTICLE INFO

Article history:
Received 27 June 2014
Received in revised form 13 August 2014
Accepted 14 August 2014
Available online 27 August 2014

Keywords:
Antidepressant-like activity
Serotonergic system
Neurotoxicity
Xanthone derivative
Piperazine derivative

ABSTRACT

Background: The studied compound: 3-chloro-5-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}-9H-xanthen-9-one dihydrochloride (HBK-6) is a new xanthone derivative. In this study we investigated its antidepressant-like properties and possible mechanism of action.
Methods: Antidepressant-like activity was evaluated in the forced swim test (FST) in mice. The influence on locomotor activity in mice was analyzed to determine whether the observed in FST effect is specific. Rotarod test was used to determine neurotoxic properties.
Results: HBK-6 reduced immobility time in mice in FST at the doses 5 and 10 mg/kg, whereas fluoxetine (FX) at 15 mg/kg, reboxetine (RX) at 10 mg/kg and bupropion (BPR) at 5 mg/kg. Joint administration of sub-effective doses of HBK-6 and FX, but not RX or BPR, reduced immobility in mice in FST. HBK-6 at the dose 5 mg/kg did not show activity in FST after pretreatment with p-chlorophenylalanine. The studied xanthone derivative at the doses 5 and 10 mg/kg did not impair motor coordination in mice.
Conclusions: We demonstrated that HBK-6 has a potent antidepressant-like activity in FST, stronger than that of FX and RX, and seems to mediate its effect through serotonergic system. Moreover, at antidepressant-like doses it does not show neurotoxic properties. Given the promising results, HBK-6 may have potential in the treatment of depression, but this needs extended studies.
© 2014 Institute of Pharmacology, Polish Academy of Sciences. Published by Elsevier Urban & Partner Sp. z o.o. All rights reserved.

Introduction

Depression is a serious mental disorder, which is becoming more and more common in developed countries. Its etiology seems to be very complex, and is not fully understood. Possible causes include genetic factors, abnormal neurotransmission in the central nervous system (CNS), neuroendocrine and immunological changes. Despite the increasing number of available antidepressants, over 30% of patients do not respond to pharmacotherapy, and only in half of them full remission can be achieved [1]. Clinical effects appearing after 2–4 weeks and numerous side effects of antidepressants are the most common reasons for drug discontinuation. It is not surprising, though, that researches are still looking for new drugs that will be more effective, have no or fewer side effects and faster onset of action.

Pharmacological investigations of xanthone derivatives date back to late sixties, and it is now well known that they possess many biological properties such as antiarrhythmic, hypotensive, anticonvulsant and antidepressant [2–4]. It has been shown that xanthones form *Kielmeyera coriacea* and *Gentiana kochiana* produce antidepressant-like effect in the rat forced swim test [5,6]. Furthermore, some xanthone derivatives inhibited monoaminoxydase A in a competitive and reversible manner, which may be responsible for their antidepressant-like activity [6,7].

As a continuation of our studies on xanthone derivatives as new drugs acting in the CNS, we investigated antidepressant-like activity, and the possible mechanism of action of a new compound: 3-chloro-5-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}-9H-xanthen-9-one dihydrochloride (HBK-6, Fig. 1) [8].

* Corresponding author.
E-mail address: karolina.pytka@uj.edu.pl (K. Pytka).

http://dx.doi.org/10.1016/j.pharep.2014.08.016
1734-1140/© 2014 Institute of Pharmacology, Polish Academy of Sciences. Published by Elsevier Urban & Partner Sp. z o.o. All rights reserved.

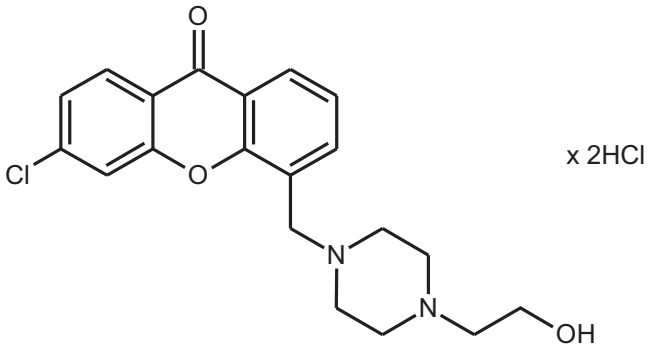

Fig. 1. Chemical structure of HBK-6.

Methods

Drug administration

The studied compound, 3-chloro-5-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}-9H-xanthen-9-one dihydrochloride (HBK-6, Fig. 1), was synthesized in the Department of Bioorganic Chemistry, Chair of Organic Chemistry, Pharmaceutical Faculty, Jagiellonian University [8]. HBK-6, fluoxetine (FX, Sigma), reboxetine (RX, Sigma) and bupropion (BPR, Sigma) were dissolved in 0.9% NaCl and injected intraperitoneally (*ip*) 30 min before each test. The control groups received 0.9% NaCl (*ip*) 30 min before the test. All solutions were injected at a volume of 10 ml/kg.

Animals

Adult male Albino-Swiss mice (CD-1, 18–21 g) were used in the experiments. The animals were kept in groups of 15 in cages at room temperature of 22 ± 2 °C, on a normal day–night cycle, and had free access to food (standard laboratory pellets) and water before experiments. The experiments were conducted between 9 a.m. and 2 p.m. Each experimental group consisted of 10, selected randomly, animals. Mice were used only once in each test, and killed immediately after the assay by cervical dislocation. All experimental procedures were approved by the I Local Ethics Committee for Experiments on Animals of the Jagiellonian University in Krakow, Poland and cared for in accordance with the Guide to the Care and Use of Experimental Animals.

Forced swim test (FST) in mice

The studies were carried out on mice according to the method described by Porsolt et al. [9]. Mice were dropped individually into glass cylinders (height 25 cm, diameter 10 cm) containing 10 cm^3 of water, maintained at 23–25 °C. The animals were left in the cylinder for 6 min, and the total immobility was measured during the last 4 min. The animal was judged to be immobile when it remained floating passively in the water.

Serotonergic depletion

To investigate the possible involvement of serotonergic system to the effect of HBK-6, mice were pretreated with tryptophan hydroxylase inhibitor – p-chlorophenylalanine (pCPA, Sigma), according to the method described by Szewczyk et al. [10]. Mice were injected *ip* with pCPA (200 mg/kg) or 0.9% NaCl (control group) once daily for 3 consecutive days. 24 h after the last pCPA administration, the mice received 0.9% NaCl or HBK-6 (5 mg/kg) 30 min before FST.

Spontaneous locomotor activity in mice

The locomotor activity in mice was measured with photoresistor actometers (Ugo Basile, Italy) connected to a counter for the recording of light-beam interruptions, and the number of light-beam crossings was counted during the 6-min session. The number of crossings of the light beams between the 2nd and the 6th min (*i.e.*, the time equal to the observation period in FST) was then recorded as the locomotor activity.

Rotarod test in mice

The test was performed according to the method described by Sałat et al. [11] with some minor modifications. Mice were trained daily for 3 days on the rotarod apparatus (rotarod apparatus, May Commat RR0711, Turkey; rod diameter: 2 cm), rotating at a constant speed of 24 rpm. During each training session, the animals were placed on a rotating rod for 3 min with an unlimited number of trials. The proper experiment was carried out at least 24 h after the final training trial. On the test day, mice were pretreated with various doses of HBK-6. Then, the animals were tested on the rotarod, revolving at 24 rpm. Motor impairment, defined as the inability to remain on the rotating rod for 1 min, was measured and expressed as the number of animals that fell off the rotating rod. ED_{50} values were calculated.

Data analysis

The data obtained were presented as means ± SEM and evaluated using one- or two-way analysis of variance (ANOVA), followed by Newman–Keuls or Bonferroni *post hoc*, respectively. Differences between groups were considered as significant if $p < 0.05$. The log–probit method described by Litchfield and Wilcoxon was used to establish ED_{50} in rotarod test [12]. ED_{50} was defined as the dose of the compound that impaired motor coordination in 50% of mice compared to control group.

Results

Antidepressant-like activity of HBK-6, FX, RX and BPR in FST in mice

HBK-6 (5 and 10 mg/kg) significantly decreased immobility (by 17% and 30%, respectively) in FST in mice [$F(4,38) = 7.108$, $p < 0.001$] (Fig. 2A). FX (15 mg/kg, Fig. 2B), RX (5 mg/kg, Fig. 2C) and BPR (2.5 mg/kg, Fig. 2D) significantly reduced immobility (by 40%, 44% and 26%, respectively) in FST in mice [$F(2,27) = 11.65$, $p < 0.001$, $F(2,27) = 5.272$, $p < 0.05$ and $F(2,27) = 4.225$, $p < 0.05$, respectively].

Effect of combined administration of sub-effective doses of HBK-6 and FX in FST in mice

The combined administration of FX (5 mg/kg) and HBK-6 (2.5 mg/kg) significantly decreased the immobility (by 37%) in the FST in mice (Fig. 3A). FX (10 mg/kg) and HBK-6 (2.5 mg/kg) had no effect on the immobility given alone (Fig. 3A). The two-way ANOVA demonstrated significant effect of FX [$F(1,36) = 17.30$, $p < 0.001$], significant effect of HBK-6 [$F(1,36) = 11.52$, $p < 0.01$], and significant interaction [$F(1,36) = 4.566$, $p < 0.05$].

Effect of combined administration of sub-effective doses of HBK-6 and RX in FST in mice

HBK-6 (2.5 mg/kg) and RX (5 mg/kg) alone or in combination had no effect on immobility in FST in mice (Fig. 3B). The two-way ANOVA demonstrated no effect of RX [$F(1,36) = 0.483$, *ns*], no effect of HBK-6 [$F(1,36) = 1.395$, *ns*], and no interaction [$F(1,36) = 1.001$, *ns*].

Download English Version:

https://daneshyari.com/en/article/2011235

Download Persian Version:

https://daneshyari.com/article/2011235

Daneshyari.com