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Short communication

Effects of morphine and methadone treatments on glutamatergic transmission in rat frontal cortex

Bartosz Bobula[1], Grzegorz Hess[1,2]

[1]Department of Physiology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

[2]Institute of Zoology, Jagiellonian University, Ingardena 6, PL 30-060 Kraków, Poland

Correspondence: Grzegorz Hess, e-mail: Hess@if-pan.krakow.pl

Abstract:
The effects of repeated administration of morphine and methadone, followed by a challenge dose of either morphine or methadone were examined *ex vivo* in rat frontal cortical slices that were prepared 1 h after final drug administration. Morphine challenge dose (5 mg/kg), administered 14 days after the end of repeated morphine pretreatment (10 mg/kg, administered 7 times) decreased both the AMPA/kainate and the NMDA components of field potentials that were evoked in cortical layer II/III by electrical stimulation. This effect did not occur either when a methadone challenge dose (2.5 mg/kg) was administered instead of morphine or after repeated morphine treatment. Moreover, after repeated methadone treatment (2.5 mg/kg, administered 7 times), neither morphine nor methadone challenge affected AMPA/kainate or NMDA components of the field potentials. These data indicate a specific effect of repeated morphine followed by morphine challenge on cortical glutamatergic transmission.

Key words:
field potential, cortical slice, AMPA receptors, NMDA receptors

Introduction

Repeated administration of opioids results in the development of sensitization, the phenomenon of an enhanced behavioral response to a given dose of an opioid [3]. In animals subjected to earlier repetitive morphine treatment, due to behavioral sensitization, a challenge dose of morphine may produce an enhanced locomotor response after periods of abstinence that last for months [15]. Sensitization is thought to play a role in the development of drug addiction and relapse [3, 7]. It has recently been shown that in addition to the effects on the profile of behavioral responses, morphine challenge given 14 days after the end of the pretreatment with morphine, induced an increase in Fos protein expression [6] in various rat brain structures [17, 18]. In particular, the induction of Fos protein in certain parts of the neocortex (including the frontal cortex) by a challenge dose of morphine was markedly enhanced by the repetitive administration of morphine.

Methadone, an agonist of μ opioid receptors, is used in substitution therapy of heroin addicts due to its potential to modify the reactions to opiates [10]. However, the cellular mechanisms of methadone action and its potential for modifying the sensitization that results from opioid treatment are not fully understood. Taracha et al. [17] have recently shown that, in contrast to morphine pretreatment, there was no en-

Tab. 1. Animal treatment schemes

Rat group (number of animals/slices)	Pretreatment[1]	Challenge[2]
control (8/25)	7 × saline	1 × saline
morphine 1 (8/27)	7 × saline	1 × morphine, 5 mg/kg
methadone 1 x (7/12)	7 × saline	1 × methadone, 2.5 mg/kg
morphine 7 (7/18)	7 × morphine, 10 mg/kg	1 × saline
methadone 7 (7/12)	7 × methadone, 2.5 mg/kg	1 × saline
morphine 7 morphine 1x (7/21)	7 × morphine, 10 mg/kg	1 × morphine, 5 mg/kg
morphine 7 methadone 1x (7/18)	7 × morphine, 10 mg/kg	1 × methadone, 2.5 mg/kg
methadone 7 methadone 1x (7/13)	7 × methadone, 2.5 mg/kg	1 × methadone, 2.5 mg/kg
methadone 7 morphine 1 (7/12)	7 × methadone, 2.5 mg/kg	1 × morphine, 5 mg/kg

[1] saline or drug administered over 7 days; [2] saline or drug administered once, 14 days after the end of the pretreatment

hancement of Fos protein expression in layer II/III of rat frontal cortex by a challenge dose of morphine after repetitive methadone administration. Furthermore, the locomotor responses of rats to the challenge were enhanced after morphine, but not methadone, treatment [18]. These findings may partly explain the beneficial effects of methadone in therapy for addiction.

It has been well established that Fos proteins (among several expression products of immediate early genes) play a role in stabilizing changes of synaptic efficacy in cortical circuits that result from synaptic plasticity processes [reviewed in: 8, 9]. Thus, it seemed conceivable that modifications in the level of c-Fos protein induction in cortical neurons by morphine treatment and reexposure to the drug [17, 18] might be reflected in functional alterations in the activity of cortical neural circuitry. Therefore, the aim of the present study was to determine the effects of single and repetitive administration of morphine and methadone on the AMPA and NMDA receptor-mediated components of field potentials that were evoked in *ex vivo* brain slices of the frontal cortex by electrical stimulation of glutamatergic pathways.

Materials and Methods

Animals

Experimental procedures were carried out in accordance with the European Community guidelines for the use of experimental animals, and national law and were approved by the local Animal Care and Use Committee. Male Wistar rats, weighing approx. 90–100 g at the beginning of the experiment, were housed in groups, subjected to a controlled light/dark cycle (light on: 7.00–19.00) and had free access to standard food and tap water.

Drugs

Morphine (Polfa, Poland) and methadone ((R,S)-methadone hydrochloride (Molteni Farmaceutici, Scandicci, Italy) were kindly provided by dr E. Taracha, Institute of Psychiatry and Neurology, Warszawa, Poland), and dissolved in water. The rats were randomized between experimental groups and were given *sc* injections of physiological saline, morphine and methadone according to the schedule and group count shown in Table 1. The experimental design and the choice of drug dosage were based on earlier reports [17, 18].

Slice preparation and recording

Brain slices were prepared 1 h after the final morphine, methadone or saline administration, as described previously [4, 5]. In brief, rats were decapitated under halothane anesthesia, their brains were quickly removed and placed in ice-cold artificial cerebrospinal fluid (ACSF) containing (in mM): 130 NaCl, 5 KCl, 2.5 $CaCl_2$, 1.3 $MgSO_4$, 1.25 KH_2PO_4, 26 $NaHCO_3$, 10 D-glucose, that was bubbled with a mixture of