Available online at www.sciencedirect.com

SCIENCE DIRECT®

Life Sciences 77 (2005) 650–655

Life Sciences

www.elsevier.com/locate/lifescie

Effects of anaesthetic agents in interference of naloxone-induced opiate-withdrawal are dose-dependent in opiate-dependent rats

Emmanuel Streel[a,b,*], Bernard Dan[c], Valérie Antoniali[a], Béatrice Clement[d], Salvatore Campanella[e], Catherine Hanak[a], Philippe Vanderlinden[d], Isy Pelc[a], Paul Verbanck[a]

[a]*CHU Brugmann (Université Libre de Bruxelles), Institut de Psychiatrie, Clinique d'Alcoologie and Toxicomanies, Brussels, Belgium*
[b]*ISEPK (Université Libre de Bruxelles) Laboratoire des Sciences de la Motricité, Brussels, Belgium*
[c]*HUDERF (Université Libre de Bruxelles) Brussels, Belgium*
[d]*CHU Brugmann (Université Libre de Bruxelles) Service d'Anesthésiologie, Brussels, Belgium*
[e]*Université Catholique de Louvain, Faculté de Psychologie et des Sciences de l'Education, Unité de Neurosciences Cognitives (NESC), Louvain-la-Neuve, Belgium*

Received 29 March 2004; accepted 8 November 2004

Abstract

In opiate-dependent rats previous studies showed that anaesthetic agents, such as chloral hydrate, midazolam and ketamine interfere with naloxone-precipitated opiate withdrawal. Each anaesthetic induces a specific pattern of interference, indicating that the interference is agent-dependent. In order to further investigate these effects and highlight a potential pharmacological basis of opiate withdrawal interference through anaesthetic agents, we hypothesized that anaesthetic-mediated interference of opiate withdrawal is also dose-dependent. Three groups of rats were compared in an experimental procedure of rapid withdrawal induction by an antagonist under anaesthesia using sub-anaesthetic dosage of midazolam, ketamine or saline. We observed that sub-anaesthetic dosage of ketamine, or midazolam, interferes significantly with opiate withdrawal expression. This brings arguments in favour of a pharmacological basis underlying rapid antagonists induction in opiate dependent rats.

Keywords: Opiate withdrawal; Rat; Anaesthetic agents; Midazolam; Ketamine

* Corresponding author. CHU Brugmann, Institut de Psychiatrie, Pl. Van Gehuchten 4, B-1020 Bruxelles, Belgium. Tel.: +32 2 4773520; fax: +32 2 4772162.
E-mail address: manu.streel@chu-brugmann.be (E. Streel).

0024-3205/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.lfs.2004.11.035

Introduction

In the management of opiate addiction, rapid naloxone/naltrexone induction under anaesthesia or various degrees of sedation has been increasingly used in the past decade in opiate-withdrawal protocols (Brewer et al., 1988; Streel and Verbanck, 2003). Some clinicians even propose domiciliary protocols (Carreno et al., 2002). As the aim of these techniques is not simply to detoxify opiate-dependent patients but also to rapidly induce antagonist-assisted abstinence, they have been conceptualised as "rapid antagonist induction" (RAI). Despite the increasing literature reporting empirical experience with various RAI procedures in humans, RAIs remain criticized (Gossop and Strang, 1997) and there is still a need for animal studies in order to clarify their effects and associated neurobiological mechanisms in opiate withdrawal interference and consequences. In a RAI model in opiate-dependant rats we showed that the use of chloral hydrate during naloxone-precipitated opiate withdrawal was associated with interference of subsequent withdrawal signs (Streel et al., 2000). Withdrawal signs initially decreased in intensity but reappeared, some of them potentiated. The use of other anaesthetic agents, midazolam (an allosteric modulator of $GABA_A$ receptor) and ketamine (an NMDA antagonist), in the modulation of opiate withdrawal in a RAI model in opiate-dependent rats indicates that each anaesthetic interferes specifically on the expression of subsequent withdrawal signs (Streel et al., 2001). We suggested a model in which these interferences could be due to a complex pharmacological interaction rather than to a residual effect of anaesthetic agents on vigilance (Streel and Verbanck, 2003). In the present study we replicated a previous experiment (Streel et al., 2001) modifying the dosage of the anaesthetic agents (midazolam and ketamine) in order to test whether interference of these agents is related to a direct pharmacological effect or a residual effect of anaesthesia on vigilance. We hypothesized that even with a significant reduction of the anaesthetic dosage (reduction of 75%) we would still observe significant interference of withdrawal signs, which would support a pharmacological basis for RAI.

Methods

Male Wistar rats weighing 200–300 g were individually housed in cages with free access to food and water for one week before the beginning of the experiment. Morphine dependence was induced by multiple injections of the drug following a specific schedule. The rats received increasing doses of morphine (subcutaneously, sc, in the scruff of the neck) three times a day (at 9 am, 12 pm and 5 pm). The doses were the following (in mg/kg): Day 1: 20, 20, 30; Day 2: 40, 40, 50 and Day 3: 50 and 100. The experiment was carried out at 5 pm on the third day of treatment. Morphine-treated rats were divided into 3 experimental groups. The KETA group (n = 10) was anaesthetized with ketamine (2.5 mg/kg, intramuscularly, IM); the MIDA group (n = 10) was anaesthetized with midazolam (0.25 mg/kg, IM) and the SALI group (n = 10) received an injection of normal saline solution. Thereafter, the three groups followed the same experimental procedure. Ten minutes after the injections (5:10 pm), the rats were injected with naloxone (1 mg/kg, sc). Two hours after the first injection (7:10 pm), the rats received a second injection of naloxone (1 mg/kg, sc). Two hours after the second injection (9:10 pm), they received a third injection of naloxone (1 mg/kg, sc). These injections of naloxone allow the precipitation of opiate withdrawal. Concerning the MIDA and the KETA groups, the first precipitation of withdrawal therefore occurred 10 minutes after they received anaesthesia. They were placed in temperature controlled conditions to avoid hypothermia. For a period of 15 minutes following each injection of