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Repeated naltrexone administration accelerates resolution of morphine somatic withdrawal signs in morphine-dependent rats

Anna Lisa Muntoni [a], Marco Diana [b,*], Gian Luigi Gessa [a]

[a] *'B.B. Brodie' Department of Neuroscience, University of Cagliari, via Porcell 4, 09124 Cagliari, Italy*
[b] *Department of Drug Sciences, University of Sassari, via Muroni 23/A, 07100 Sassari, Italy*

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Abstract

Morphine-dependent rats were divided into two subgroups. The first was allowed to develop a spontaneous withdrawal syndrome which was still present 33 h after the last morphine administration. The second subgroup received five injections of naltrexone. While the first two injections of naltrexone precipitated a marked somatic withdrawal syndrome, subsequent naltrexone failed to worsen the somatic signs. 24 h after the last morphine administration, naltrexone was completely ineffective. It is concluded that naltrexone shortens the duration of the morphine somatic withdrawal signs in dependent rats.

Keywords: Opiate detoxification; Withdrawal syndrome; Naltrexone

Opiate dependence requires the disappearance of the withdrawal syndrome before pharmacological treatments with opiate antagonists such as naltrexone, commonly used to prevent relapse, can be administered (Gonzales and Brogden, 1988). Although general agreement exists among experts that the major problem is posed by psychological aspects of withdrawal (Phillips et al., 1986), the somatic manifestations of withdrawal are a serious obstacle in the way of abstinence from opiates. Recently, a new approach has been suggested which could be useful in humans addicted to opiates. This treatment consists of repeated administration of naltrexone under conditions of mild anesthesia obtained with midazolam (Legarda and Gossop, 1994). According to the authors, this treatment should drastically reduce the duration of opiate withdrawal, thus providing a first step toward a drug-free state.

The reported shortening of the somatic withdrawal obtained with this protocol is an appealing objective in the treatment of opiate dependence. Consequently, we sought to determine if naltrexone administered repeatedly to morphine-dependent rats does indeed produce shortening of the somatic signs of opiate withdrawal. The use of anesthesia was left out from the present protocol in order to evaluate behaviorally the intensity and duration of morphine somatic withdrawal.

Male Sprague-Dawley (Charles River, Como, Italy) rats weighing 200–225 g at the beginning of treatment were used. The rats were made dependent on morphine using the schedule proposed by Acquas and Di Chiara (1992).

On the 14th day from the start of treatment, morphine-dependent rats were divided into two subgroups. The first subgroup ($n = 7$) was left to develop a spontaneous withdrawal syndrome. Withdrawal severity was assessed according to a point-scoring technique (Frederickson and Smits, 1973) 2, 7, 24, 27 and 33 h from the last morphine administration, for both groups.

Immediately before each behavioral assessment, animals assigned to the second subgroup ($n = 6$) were challenged with an injection of the opiate antagonist, naltrexone (10 mg/kg i.p.), while the first subgroup received a corresponding volume of saline.

As shown in Fig. 1, the physical signs of spontaneous withdrawal and of naltrexone-precipitated withdrawal syndrome show a different time course ($P < 0.005$ vs. saline-treated rats, one-way analysis of variance (ANOVA), with multiple dependent variables; logarithms of the values were used for statistical analysis.

The behavioral scores of rats belonging to the first subgroup gradually increased, to peak at 24 h from the last morphine administration, then slowly decreased.

* Corresponding author. Tel.: (39) (79) 228717; fax: (39) (79) 228715.

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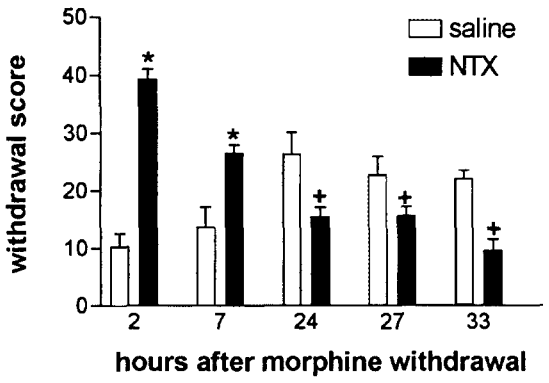

Fig. 1. Time course of behavioral withdrawal scores of rats developing spontaneous withdrawal syndrome (saline) and naltrexone-precipitated withdrawal (NTX). Behavioral assessments were performed at different time points, as indicated, after the last morphine administration. $P < 0.002$ (Newman-Keuls test) vs. saline-treated controls at 2 and 7 h from the last morphine administration; $^{+}P < 0.01$ (Newman-Keuls test) vs. NTX-treated rats at 2 and 7 h from the last morphine administration.

On the other hand, abstinence scores of naltrexone-treated rats increased, as expected, immediately after the first two naltrexone administrations, 2 and 7 h after morphine. Subsequent injections of naltrexone (24, 27 and 33 h after the last morphine administration, respectively), however, were completely ineffective (Fig. 1).

These results demonstrate that repeated naltrexone administration shortens the duration of morphine somatic withdrawal signs in dependent rats. Given that one of the main problems in opiate detoxification is the duration of this process, the reported shortened resolution of the somatic withdrawal syndrome is encouraging. On the other hand, some authors had previously shown that the combined use of clonidine and naltrexone may compress the process of opiate detoxification (Charney et al., 1986), thus leading the way for an additional role of naltrexone. While naltrexone had been used so far as maintenance aid for long-term therapies of detoxified addicts, to extinguish opioid-seeking behavior, the present experiments support the use of naltrexone in not yet detoxified addicts.

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