

MORPHINE WITHDRAWAL-INDUCED INCREASE IN EXCITABILITY OF MEDIUM SPINY NEURONS IN THE NUCLEUS ACCUMBENS

Lintas Alessandra, Panin Francesca, Marco Diana

“G. Minardi” Laboratory of Cognitive Neuroscience, Department of Drug Sciences, via Muroni 23/a, University of Sassari, 07100 Sassari, Italy

Among the various neurotransmitter systems influenced by morphine administration the dopaminergic (DAergic) system is well established to play a pivotal role. Indeed, it is well documented how this system, especially its mesolimbic subdivision, is involved in drug-induced reward (1), and in opiate addiction (2). Morphine withdrawal produces a hypofunction of mesencephalic dopamine neurons that impinge upon medium spiny neurons (MSN) of the forebrain (3). The MSN are the principal post-synaptic target of DAergic afferents from the Ventral Tegmental Area (VTA) (4). The present study was designed to investigate possible electrophysiological modification of MSNs during withdrawal after chronic morphine administration and their time course.

Male albino rats were used and subdivided in two groups: chronically treated (see 5) with morphine and relative controls (chronic vehicle). After chronic administration (from 10 to 140 mg/kg of morphine twice a day over 14 days at escalating doses), putative MSN of the Nacc were identified by antidromic activation from the VTA. Through the use of the cells/track method, a “population study” was conducted in spontaneously and pharmacologically (naltrexone 5mg/kg) withdrawn rats, at various times (1, 3, 7, 14 days). Moreover the effect of an acute morphine (4 mg/kg) challenge was evaluated, on the percentage of evoked responses to basolateral amygdala (BLA) stimulation, and on the cells/track index. Briefly, by passing the recording electrode different times through the Nacc (tracks), identified cells can be counted to obtain the cells/track index. Results show that cells/track was increased in spontaneously withdrawn rats as compared with chronic saline controls; this effect persists beyond 14 days. A qualitatively similar but larger increment was observed after naltrexone administration. In addition, a decrease in these cells/track was detected after acute morphine (i.v.). Our results show that excitability of MSN is increased during morphine withdrawal as revealed by the cells/track index. In addition, the increased index observed upon withdrawal persists over time. Coherently acute treatment with morphine (4mg/kg) decreased excitability. The results suggest that MSN of Nacc show an increased excitability during morphine withdrawal which persists over time, thereby supporting a major role played by these neurons in opiate addiction mechanisms. Collectively, the present results support recent theories (6) which indicate in a hypodopaminergic state a cardinal feature of addiction.

References:

- (1) Di Chiara G, Imperato A (1988) Proc Natl Acad Sci U S A. 85(14): 5274-5278.
- (2) Diana M, Muntoni AL, Pistis M, Melis M, Gessa GL (1999) Eur J Neurosci 11(3): 1037-1041.
- (3) Diana M, Pistis M, Muntoni AL, Gessa GL (1995) J Pharm Exp Ther 272(2): 781-785.
- (4) Smith AD, Bolam JP (1990) Trends Neurosci 13(7): 259-265.
- (5) Acquas E, Di Chiara G (1992) J Neurochem 58(5): 1620-1625.
- (6) Melis M, Spiga S, Diana M (2005) Int Rev Neurobiol 63: 101-152.