The Role of Nitric Oxide Synthase Inhibition in Nucleus Accumbens Core Region on Naloxone Induced Morphine Withdrawal Signs in Rats

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Objective:

There is considerable evidence suggesting that nitric oxide (NO) pathways may have a role in the onset of morphine withdrawal symptoms (Yananli et al. 2007) and it was shown that nitric oxide synthase (NOS) inhibitors diminishes some signs of naloxone precipitated morphine withdrawal (Adams et al., 1993). NO is synthesized in nucleus accumbens (Nacc) by aspiny interneurons containing neuronal NOS (nNOS), and this nNOS activity is thought to be regulated by dopaminergic and glutamatergic transmission (Hoque and West, 2011). Nacc is a key component of the reward pathway that is common for many drugs of abuse including opioids, and changes in neurotransmission in this region is thought to have a role in morphine withdrawal (Chieng and Williams, 1998). This study was designed to evaluate the effects of NOS inhibition in Nacc core region by NG-nitro-L-arginine methyl ester (L-NAME) on naloxone induced morphine withdrawal signs in rats.

Method:

Male and female Sprague-Dawley rats weighing 250-300 g supplied from Marmara University Experimental Research and Animal Center were used. All the rats were housed in a quiet and temperature controlled room (21±3°C) maintained on 12-h light/dark cycle (07:00-19:00 light) and were allowed food and water ad libitum. Rats were anesthetized with intra-peritoneal (i.p) ketamine (100 mg/kg) and xysilazine (10 mg/kg) and 2 guide cannulae were implanted into bilateral Nacc core region according to the coordinates provided from the rat brain atlas (Paxinos and Watson, 2007). Three morphine pellets that each contained 75 mg of morphine base, were implanted subcutaneously in the scapular area under light ether anesthesia on successive three days, namely one pellet on the first and two on the third day. 48 hours after the last pellet implantation, either LNAME (1.5µg/side) or artificial cerebrospinal fluid (aCSF) microinjection, in a volume of 0.5µl, applied to bilateral Nacc core region. Shortly after, rats were received i.p. naloxone (2 mg/kg) injection and were put into plexiglass locomotor activity cage where the behavioral signs of naloxone induced morphine withdrawal such as wet dog shakes, jumping, defecation, teeth chattering, ptosis and weight loss were observed and quantified for 15 minutes with concomittant locomotor activity measurement.

Results:

LNAME microinjection into bilateral NAcc decreased the number of wet dog shakes as compared to aCSF microinjection. However, there were no differences in other withdrawal signs between these two groups. Following naloxone injection, there was an increase in locomotor activity according to basal value in both groups, but this increase was diminished in rats that received LNAME microinjection.

Conclusion:

These results suggested that NOS activity in Nacc core region may have a role in the onset and expression of some of the naloxone precipitated opiate withdrawal signs.

References:


