TIME-DEPENDENT MORPHOLOGICAL AND BIOCHEMICAL CHANGES DURING MORPHINE WITHDRAWAL IN THE RAT NUCLEUS ACCUMBENS

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A reduction in dopamine neuronal function is a neurobiological substrate of opiate withdrawal. In the present study we assessed the morphological and biochemical effects of morphine dependence and withdrawal on nucleus accumbens shell and core medium spiny neurons, post-synaptic target of the hypofunctioning dopaminergic system. By means of Golgi-Cox staining and morphological analysis, we evaluated the consequences of morphine withdrawal (spontaneous and pharmacologically precipitated with the opiate antagonist naloxone) on spines' density of MSN of the nucleus accumbens shell and core. Our results indicate that morphine withdrawal (both spontaneous and pharmacologically precipitated) reduces the number of spines of 2nd order dendrites in shell but not core of the nucleus accumbens while leaving unaffected spines of 3rd order dendrites of both shell and core of the nucleus accumbens. In order to study the reversibility over time of these effects we investigated the same measures at 3, 7 and 14 days of withdrawal and found the reduction to be reversible over time since spines' density of 2nd order dendrites was still significantly reduced in the shell of the nucleus accumbens after three days but recovered to control values at 14 days of withdrawal. In order to test the hypothesis that the reduction of spine's density in the nucleus accumbens shell could be attributed to the hypofunctioning dopaminergic system, we studied the consequences of the administration of reserpine (5 mg/kg) on spine's density in the nucleus accumbens shell and core. The results of this experiment indicated that following reserpine there is a time-dependent reduction of spines on 2nd order dendrites both in the shell and core of the nucleus accumbens. Finally, we also determined, during spontaneous and naloxone-precipitated withdrawal, the activation of extracellular signal regulated kinases (ERKs) by immunoistochemical / densitometric assessment. The results of these experiments revealed a reduction of phosphoERK density/neuron in the shell, but not core, that peaked at 1 day of spontaneous and naloxone-precipitated withdrawal and fully recovered to control values at 14 days of withdrawal. Overall, these results suggest that morphine withdrawal is associated to dramatic but reversible morphological changes of synapses in the shell of the nucleus accumbens that might be related to the reduction of the dopaminergic function. These results also indicate that the morphological changes seen during withdrawal parallel, in time-locked manner, the reduction of phosphoERK density in NAc shell MSN suggesting that ERKs activation may play a role in the modulation of synaptic plasticity.