Expression of NMDA receptor subunits in human peripheral blood lymphocytes in opioid addiction

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ABSTRACT

Glutamate receptors especially the N-methyl-D-aspartate (NMDA)-activated ones have a key role in the development and maintenance of opioid addiction. It has been proposed that the neurotransmitter receptors expression in peripheral blood lymphocytes may be parallel to their expression state in the brain. This study was designed to evaluate the possibility of using the mRNA expression state of NR2A and NR3A subunits of NMDA receptors in human peripheral blood lymphocytes as a peripheral marker in opioid addiction studies. Four groups, each comprising of 20 male individuals participated in the study: opioid addicts, methadone maintained patients, long-term abstinent former opioid addicts, and non-addicted control subjects. Real-time PCR method was used to investigate the mRNA expression level of NR2A and NR3A subunits of NMDA receptors in peripheral blood lymphocytes of all groups. Our data indicated that the mRNA expression of NR2A subunit of NMDA receptors in all three test groups was not statistically different from control subjects. However, the NR3A subunit expression was significantly down-regulated in abstinent subjects reaching 0.14 the amount of the control group. The expression of NR3A subunit was not significantly changed in addicted and methadone maintained individuals in comparison to control subjects. It is concluded that the deficiency in expression of NR3A subunit of NMDA glutamate receptors detected by a peripheral marker may be a risk factor making individuals vulnerable for opioid addiction.

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1. Introduction

Glutamate, the main excitatory neurotransmitter in the mammalian central nervous system, has a major role in the addictive properties of opioids. The neurotransmitter is widely distributed in different parts of the brain especially the mesocorticolimbic pathway (Chuhma et al., 2009; Gass and Olive, 2008). The cell bodies of the pathway are located in the ventral tegmental area and the axons project primarily to the nucleus accumbens and also to other sites such as the prefrontal cortex, amygdala and hypothalamus. Stimulation of the pathway by addictive drugs and natural reinforcers such as food or sex leads to dopamine release in the nucleus accumbens which results in pleasure and reward (Spanagel and Weiss, 1999).

Glutamatergic projections and glutamate receptors are present in many parts of the reward pathway. For example, the nucleus accumbens receives glutamatergic input from the frontal cortex, amygdala, hippocampus and thalamus which may represent the anatomical interaction of dopamine and glutamate in regulating the addictive properties of drugs (Tzschentke and Schmidt, 2003). Glutamate acts via both ionotropic and metabotropic groups of receptors. The N-methyl-D-aspartate (NMDA) receptor is an ionotropic glutamate receptor which is highly permeable to calcium and is composed of seven different subunits, named NR1, NR2A–D, NR3A and NR3B. It has been found that the NMDA receptors containing NR3 subunits display reduced calcium permeability and post synaptic currents in comparison to conventional NR1/NR2 assemblies (Kew and Kemp, 2005).

In addition to neurons, NMDA-activated glutamate receptors are found in other cell types such as lymphocytes (Boldyrev et al., 2005) where they may modulate the activity of these cells (Miglio et al., 2005). Recent findings have indicated that NR1 and NR2 subunits of the NMDA receptor are expressed in the human peripheral blood lymphocytes (Biermann et al., 2007).

Previous studies in rodents have revealed that the expression pattern of NMDA receptor subunits may alter in different parts of the...