Role of nitric oxide in cocaine effects

The observation that nNOS is linked to NMDAR subunits led to studies on therole of nNOS in the effects of cocaine. Chronic cocaine administration increased NOSactivity in cerebral cortex, cerebellum, midbrain, hypothalamus, hippocampus, amygdalaand spinal cord of Swiss-Webster mice (Bhargava & Kumar, 1997). Acute systemicadministration of cocaine facilitated NO efflux in the rat prefrontal cortex via a nNOSdependentmechanism since this effect was attenuated by the nNOS inhibitor 7-nitroindazole (7-NI) (Sammut & West, 2008). The increase in NO efflux following acutecocaine administration is mediated through interaction between DA D1 receptor andNMDAR in the dorsal striatum (Lee et al.

, 2011). Evidence supporting the involvement of NO signaling in cocaine reward emergedfrom cocaine self-administration studies. The non-selective NOS inhibitor Nw-Nitro-Largininemethyl ester (L-NAME) dose-dependently suppressed both the maintenance ofcocaine self-administration and the absolute reward magnitude of cocaine (Pulvirenti etal., 1996). Additionally, L-NAME significantly reduced drug-seeking behavior followingabrupt cessation of drug availability as well as attenuated the reinstatement of cocaineself-administration in response to a priming injection of cocaine (Orsini et al., 2002). Likewise, the nNOS inhibitor 7-NI prevented cocaine-induced alterations in medialprefrontal cortex excitability and decreased cocaine self-administration in rats (Collins &Kantak, 2002) supporting the role of nNOS in these effects. NO signaling has a role in cocaine-induced associative learning.

Results fromCPP experiments support the role of NO signaling in the motivational effects of cocaine. Studies from our laboratory have shown that

both pharmacological (7-NI) and genetic(nNOS KO) manipulations of nNOS provided resistance to cocaine-induced CPP (Itzhaket al., 1998). It was also shown that cocaine CPP can be extinguished by disrupting drugassociatedmemory reconsolidation; a process whereby retrieval of a previously storedmemory becomes labile and subject to manipulation. This process was found to benNOS-dependent because a) administration of 7-NI to WT mice upon retrieval ofcocaine-CPP impaired further expression of place preference, and b) administration of theNO donor molsidomine to nNOS KO after retrieval of cocaine-associated memoryprolonged CPP expression, suggesting disruption and strengthening of memoryreconsolidation, respectively (Itzhak & Anderson, 2007). A subsequent experimentshowed that not only does treatment with MK-801 or 7-NI independently, disruptcocaine-associated memory reconsolidation, but they also provided resistance toreinstatement of CPP following a priming dose of cocaine (Itzhak, 2008).

Overall, resultssuggest the role of NO signaling in cocaine reward and cocaine-associated memory; thusmanipulation of this pathway may afford resistance to cocaine-seeking behavior.