Stress-induced reinstatement of fix-c and esc-c memory

Vulnerability to relapse following prolonged periods of abstinence presents amajor challenge to combating drug addiction. Stress is an unavoidable part of life and amajor contributor to relapse to drug use. However, a thorough understanding of theneural mechanisms that sub-serve stress-mediated relapse is lacking. In Chapter 4, thecontribution of different signaling molecules to stress-induced reinstatement of Fix-C andEsc-C CPP was investigated. While antagonism of NMDAR and inhibition of nNOSeffectively attenuated forced swim-induced reinstatement of Fix-C CPP, thesemanipulations had no effect on Esc-C CPP (Fig. 4.

1 and 4. 3). Thus, like the acquisitionand reconsolidation of Fix-C memory, stress-induced reinstatement of Fix-C memory isNO-dependent while Esc-C memory is NO-independent. My studies add to the list ofsignaling molecules that play a role in stress-induced reinstatement of Fix-C CPP. However, none of the test drugs investigated that successfully attenuated stress-inducedreinstatement of Fix-C was effective against Esc-C CPP. Therefore, my studies point tothe existence of additional signaling molecules that contribute to stress-inducedreinstatement of Esc-C CPP.

Proposed model for the development of Fix-C and Esc-C memoryFigure 5. 1 proposes a model for the contribution of different signaling pathwaysto the formation of Fix-C and Esc-C memory. Fix-C and Esc-C memory results fromincreased protein expression levels of NR2B subunit of the NMDAR. However, NR2B ismarkedly elevated in mice conditioned by Esc-C compared to mice conditioned by Fix-C. NR2B-containing NMDARs allow greater calcium entry thus elevated NR2B levels inEsc-C conditioned mice allow for increased calcium influx upon NMDAR activation byglutamate. My findings

show that Fix-C memory acquisition, reconsolidation and stressinducedreinstatement can be blocked by inhibiting nNOS but Esc-C memory remainsunperturbed. With respect to the Fix-C model, calcium influx activates calmodulin whichmediates nNOS-induced increases in NO levels.

NO stimulates soluble guanylate cyclase(sGC) which leads to cGMP-mediated activation of protein kinase G (PKG) whichsubsequently contributes to the phosphorylation of ERK. With respect to Esc-C memory, evidence suggests that the NR2B subunit of NMDAR has potential to carry greatercalcium current per unit charge (Sobcyk et al., 2005) which may confer a greaterinfluence on downstream signaling cascades that affect synaptic plasticity and learningand memory such as the NMDAR-RasGRF1-MEK-ERK pathway (Krapivinsky et al., 2003).

Since RasGRF1 specifically binds the NR2B subunit of the NMDAR, it couplesthe activity of ERK with NR2B-containing NMDARs (Krapvinisky et al., 2003). Mystudies show that inhibition of MEK, the ERK kinase, disrupted reconsolidation of Esc-Cmemory but had no effect on Fix-C memory (Fig. 2. 5). Thus the MEK-ERK pathwayplays a role in Esc-C memory. While the nNOS signaling pathway may also be activatedin response to training by Esc-C, it appears that other signaling pathways includingNMDAR-MEK-ERK signaling plays a more behaviorally significant role in thedevelopment of Esc-C CPP.

Additionally, though both NO-cGMP-PKG and MEKsignaling pathways converge at the level of ERK (Ota et al., 2008) it is conceivable thatthe contribution of each pathway to drug memory is dependent on cocaine conditioningschedule. The differential activation of ERK could result in

different degrees ofactivation of molecules downstream of ERK including cAMP response element bindingprotein (CREB). CREB is a known mediator of synaptic plasticity and the generation ofnew synapses through upregulation of gene expression which subsequently contribute tomemory strength.

Thus increased phosphorylation of CREB (pCREB) provides greaterpropensity for rapid metaplasticity to strengthen drug-associated synapses associated with‘ strong’ Esc-C memory.