The effect of phosphodiesterase inhibitors on the extinction of cocaine-induced c...

everal phosphodiesterase inhibitors (PDEi) improve cognition, suggesting thatan increase in brain cAMP and cGMP facilitates learning and memory. Since extinctionof drug seeking behavior requires associative learning, consolidation and formation ofnew memory, the present study investigated the efficacy of three different PDEi inextinction of cocaine-induced conditioned place preference (CPP) in B6129S mice.

Micewere conditioned by escalating doses of cocaine which was resistant to extinction by freeexploration. Immediately following each extinction session mice received a)saline/vehicle, b) rolipram (PDE4 inhibitor), c) BAY-73-6691 (PDE9 inhibitor) or d)papaverine (PDE10A inhibitor). Mice that received saline/vehicle during extinctiontraining showed no reduction in CPP for > 10 days. BAY-73-6691 a) dose-dependentlyincreased cGMP in hippocampus and amygdala b) significantly facilitated extinction andc) diminished the reinstatement of cocaine CPP. Rolipram, which selectively increasedbrain cAMP levels, and papaverine which caused increases in both cAMP and cGMPlevels, had no significant effect on extinction of cocaine CPP. Results suggest thatincrease in hippocampal and amygdalar cGMP levels via blockade of PDE9 has aprominent role in the consolidation of extinction learning. BackgroundThe administration of a drug that changes the affective state of the organism in aspecific context triggers an associative learning process and the formation of long-termmemory (LTM). The expression of conditioned place preference (CPP) is viewed as a testfor reactivity to drug-associated conditioned stimulus (CS); this test has validity for cuereactivityin human drug users.

The CPP paradigm has also been used to investigateextinction of “ drug-seeking behavior” and reinstatement of conditioned response (Aguilaret al., 2009; Itzhak & Martin, 2002; Parker & McDonald, 2000; Mueller & Stewart, 2000; Mueller et al., 2002). Interestingly, reinstatement of cocaine CPP followingextinction is a drug-specific phenomenon that can be triggered only by drugs that share asimilar mechanism of action with that of cocaine (Itzhak & Martin, 2002). Therefore, thereinstatement of place preference, like the reinstatement of drug self-administrationpresents a meaningful resource for the study of relapse. Animal and human studiessuggest that re-exposure to a low dose of psychostimulants, opiates or alcohol, followingabstinence or extinction of drug use, may cause relapse (Shaham et al., 2003). It istherefore critical to develop pharmacotherapies and behavioral practices by whichextinction of drug seeking behavior will ultimately result in resistance to both drugassociatedcues and drug-priming.

Extinction learning by “ exposure therapy” is thought to be essential for themanagement of drug addiction (Carter & Tiffany, 1999; Powell et al., 1993; Siegel &Ramos, 2002). Extinction typically requires long or multiple re-exposures to a CS(Nader, 2003; Power et al., 2006). Results from fear conditioning studies suggest that theextinction process does not eliminate or cause ‘ unlearning’ of the initial conditionedresponse; rather, the organism learns that the CS no longer elicits the previous stimulus(Bouton, 2002; 2004; Havermans & Jansens, 2003). Thus, extinction requires associativelearning, consolidation and formation of new memory (Milad & Quirk, 2002; Santini etal., 2001). Through the activation of their respective kinases (PKA and PKG), cyclicnucleotide (cAMP and cGMP) signaling

pathways are important regulators of neuralfunction and synaptic homeostasis (Bales et al.

, 2010). While adenylyl cyclase (AC) andguanylyl cyclase (GC) generate the second messengers cAMP and cGMP respectively, phosphodiesterases (PDEs) hydrolyze these cyclic nucleotides into their inactivemonophosphates, 5'-AMP and 5'-GMP, and thereby contribute to the regulation of theirintracellular levels (Essayan, 2001). Eleven different families of mammalian PDE's havebeen identified in the CNS and periphery. All neurons express multiple PDEs whichdiffer in cyclic nucleotide specificity, affinity, regulatory control and subcellulardistribution (Bender & Beavo, 2006; Blokland et al., 2006; Boswell-Smith et al., 2006; Menniti et al.

, 2006). The differential localization of PDEs in the CNS and periphery determine howeffective phosphodiesterase inhibitors (PDEi) are at regulating different processes. BrainPDEs include PDE1, PDE2, PDE4, PDE5, PDE9, PDE10 and PDE11. PDE4 is widelydistributed throughout the brain (Bender & Beavo, 2006). The PDE4 inhibitor rolipramhas been used as an anti-inflammatory and has shown antipsychotic-like therapeuticeffects (Kelly et al., 2007). Rolipram enhances learning and memory in variousparadigms (Cheng et al.

, 2010; Monti et al., 2006; Rose et al., 2005; Tully et al.

, 2003; Zhang & O'Donnell, 2000), but unexpectedly it disturbed expression and extinction ofconditioned fear in mice (Mueller et al., 2010). PDE9 is highly localized in all sub-areasof the hippocampus (van Staveren et al., 2002; 2004; Reyes-Irisarri et al., 2007) and thespecific PDE9 inhibitor BAY-

73-6691 improves learning and memory in rodents (vander Staay et al., 2008). PDE10A is densely localized in the striatum but less in thehippocampus (Seeger et al., 2003).

Papaverine is a specific inhibitor of PDE10A thatincreased levels of cAMP and cGMP (Siuciak et al., 2006) and improved phencyclidineinducedcognitive deficits in rats (Rodefer et al., 2005). The use of selective PDEi as potential cognitive enhancers is suggested by studiesin which PDEi facilitated learning and memory in animal models with experimentallyinduced learning and memory deficits (Bender & Beavo, 2006; Blokland et al.

, 2006; Boswell-Smith et al., 2006; Menniti et al., 2006). However, it is unclear whetherselective PDEi facilitate learning and memory in subjects with no cognitive impairments. Therefore, the effects of the PDEi on extinction learning may be different than theireffects on improving learning following cognitive deficits.

The hippocampus and amygdala are implicated in spatial/contextual andemotional/cued memory, respectively. We hypothesized that increases in hippocampaland amygdalar cyclic nucleotide levels through the action of PDE inhibitors will facilitateextinction learning of cocaine-induced place preference. We sought to investigate PDEinhibitors with different specificities to cAMP and cGMP in order to determine which ifany group of PDE inhibitors has a more prominent role in the consolidation of extinctionlearning. We first determined how cyclic nucleotide levels were affected in thehippocampus and amygdala in response to a PDE4 (cAMP specific) inhibitor rolipram, aPDE9 (cGMP specific) inhibitor BAY-73-6691 and a PDE10A (dual specificity)

inhibitorpapaverine. Then, the efficacies of these PDE inhibitors to extinguish and preventreinstatement of cocaine CPP were investigated.

We report that of the three PDEinhibitors only BAY-73-6691, which increased hippocampal and amygdalar cGMPlevels, induced the extinction and attenuated the reinstatement of cocaine placepreference.