FACILITATION OF CONDITIONED REINSTATEMENT OF COCAINE-SEEKING FOLLOWING CENTRAL ADMINISTRATION OF NEUROPEPTIDE S.

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Cocaine addiction is a chronic relapsing disorder characterized by compulsive drug-seeking and use. Environmental conditioning factors have been recognized as one of the major determinants of relapse in abstinent individuals. The significance of these factors for relapse risk is well documented also in the animal literature where using various reinstatement paradigms it has consistently been shown that presentation of cues predictive of cocaine availability elicit reinstatement of drug-seeking in drug-free animals. Recently, a new arousal promoting neuropeptide, named Neuropeptide S (NPS), that binds to its cognate Gq protein coupled receptor and identified as NPSR receptor has been deorphanized. In situ hybridization experiments showed abundant expression of NPSR receptor mRNA in brain regions (i.e., amygdala, hippocampus and lateral hypothalamus), that are known for their role in the regulation of conditioned reinstatement of cocaine seeking. For this reason, in the present study we sought to investigate the effect of NPS administration on this cocaine-related behaviour. Rats were trained to self-administer cocaine and to associate distinct discriminative stimuli with intravenous (IV) drug availability (S^+) or non-availability (S^-; IV saline). Rats then, were subjected to daily extinction sessions during which cocaine, saline, and the discriminative stimuli were withheld until animals reached an extinction criterion of < 6 presses/h which required on average 10 days. Re-exposure to the cocaine S^+ alone, was sufficient to reinstate cocaine seeking (47.83 $\pm$ 11.74, $p<0.01$). Treatment with NPS (0.0, 1.0 and 2.0 nmol/rat) given intracerebroventricularly (ICV) 10 min before the reinstatement elicited a significant potentiation of cue effects and operant responding at previously active lever was significantly increased (NPS 1.0 nmol: 55.1 $\pm$ 10.7 NS; NPS 2.0 nmol: 85,7 $\pm$ 15.7, $p<0.05$). Responding at the inactive lever was very low and was not affected by drug treatment. In a subsequent experiment, NPS (0.0, 0.1 and 0.5 nmol/rat) was bilaterally injected into the lateral hypothalamus (LH). Following presentation of cocaine cues rats treated with NPS vehicle showed a significant reinstatement of cocaine seeking (23.7±5.3, $p<0.01$). Peptide administration significantly increased the effect of cues (NPS 0.1 nmol: 62.8 $\pm$ 14.2 $p<0.05$; NPS 0.5 nmol: 92.5 $\pm$ 18.5, $p<0.01$). Overall the results demonstrate that activation of NPS receptors facilitates relapse to cocaine seeking induced by environmental conditioning factors and the LH is an important brain site of action for this effect of the peptide. NPS receptor antagonists have not been developed yet, but based on the present data it is interesting to evaluate whether this class of compounds might be of potential efficacy in the treatment of cocaine relapse. (Supported by PRIN 2006 to RC).