NEUROPEPTIDE S: A NEW NEUROTRASMITTER SYSTEM INVOLVED IN RELAPSE TO ALCOHOL-SEEKING BEHAVIOUR

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Alcoholism is a chronic relapsing disorder characterized by compulsive drug-seeking and use. Stress and environmental conditioning have been recognized as the three major determinants of relapse in abstinent individuals. 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 alcohol abuse and reinstatement of alcohol seeking. In the present study we sought, therefore, to investigate the effect of NPS on ethanol self-administration and relapse. Wistar rats were trained to operantly self-administer 10% ethanol until stable baseline of responding was established. At this point, rats received intracerebroventricular (ICV) injection of NPS (0.0, 1.0 and 2.0 nmol/rat) prior to ethanol self-administration.. Results showed no effect of drug treatment ($P>0.05$). In a subsequent series of experiments the ability of NPS to modulate reinstatement of alcohol seeking induced by environmental conditioning factors or stress was tested. For conditioned reinstatement Wistar rats were trained to self-administer 10% ethanol or water in 30 min daily session on a FR-1. Ethanol availability was signalled by orange odour (S^+) that served as a discriminative stimulus and by activation of the house light for 1 s (CS^+) contingent to each lever pressing. For water, anise odour (S^-) and 1 s white noise (CS^-) were used. Discrimination was followed by an extinction phase during which lever presses did not result in the delivery of ethanol, water or presentation of the corresponding cues. After 15 extinction sessions animal responding was below 10. Re-exposure to the alcohol cues (S^+/CS^+) but not water cues (S^-/CS^-) reinstated responding ($p<0.01$). ICV treatment with NPS (0.0, 1.0, 2.0 and 4.0 nmol/rat) significantly increased cues induced reinstatement. For stress-induced relapse, after acquisition of ethanol self-administration animals were subjected to an extinction phase (15 days) and then tested for stress- (15 min intermittent foot shock, 0,6 mA) induced relapse. Stress elicited a significant reinstatement of ethanol seeking ($p<0.05$). Treatment with NPS (0.0, 1.0 and 2.0 nmol/rat) prior to stress presentation significantly increased alcohol seeking Overall the results demonstrate that activation of NPS receptors does not affect ethanol intake but facilitates relapse to alcohol seeking induced by environmental conditioning factors and stress. (Supported by PRIN 2006 to RC).