

Modulation of traumatic memory acquisition and recall via prefrontal cortical dopamine d4 and d1 receptor transmission differentially controls opiate reward sensitivity: implications for addiction comorbidity in post-traumatic stress disorder

Background

PTSD and opiate addiction share strong co-morbidity and the inability to suppress obtrusive memory recall related to either stressful or rewarding experiences may be an underlying neuropsychological feature triggering PTSD and/or addiction. Our previous research has shown that dopamine (DA) transmission in the prefrontal cortex (PFC) strongly modulates emotional memory formation: activation of the DA D4 receptor (D4R) strongly potentiates the emotional salience of normally non-salient fear memories whereas DA D1 receptor (D1R) activation blocks the behavioural recall of fear memory. Thus, while intra-PFC D4 transmission strongly controls the acquisition of emotional memory, D1 transmission is selectively involved in the recall phase of emotional memory processing. Therefore, we are aiming to test the role of PFC dopamine transmission in emotional memory regulation and opiate sensitivity.

Methods

Using a pre-clinical model of PTSD in rats, we examined if recall of associative fear memory would increase subjects' sensitivity and vulnerability to morphine addiction. We also examined if blocking traumatic memory recall with PFC D1R stimulation may block this effect and if artificially creating a fear memory with PFC D4R stimulation would increase morphine reward sensitivity. Using an olfactory fear conditioning paradigm, we conditioned salient or non-salient associative fear memories by delivering supra-threshold (0.8 mA) vs. sub-threshold (0.4 mA) foot shock conditioning cues, and tested if recalling these memories increased sensitivity to morphine's rewarding properties, measured in a conditioned place preference (CPP) paradigm. We then examined the effects of intra-PFC DA D1R/D4R activation on expression and acquisition phases of associative fear memories and the subsequent influence on morphine reward sensitivity.

Results

Rats receiving supra-threshold fear conditioning showed strong associative fear memories and strongly potentiated morphine reward sensitivity. PFC activation of D1 receptor transmission with SKF 81297 (10-100 ng), dose-dependently blocked the recall of fear memory and similarly blocked the potentiation of morphine reward CPP through a cyclic AMP-dependent molecular pathway. In contrast, PFC D4 activation with PD-168077 (50 ng) during memory acquisition, created false fear memories in rats receiving sub-threshold foot shock. Remarkably, D4-mediated potentiation of normally non-salient fear memories also caused a dramatic potentiation in morphine reward sensitivity.

Conclusion & Interdisciplinary Reflection

Our findings have important implications for the role of the PFC DA receptor transmission in PTSD-related traumatic memory acquisition and recall and suggest that dysregulation of PFC DA transmission may underlie co-morbidity between PTSD and opiate addiction.