Doctoral Thesis

Mesocorticolimbic dopamine system in fear conditioning

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MESOCORTICOLIMBIC DOPAMINE SYSTEM IN FEAR CONDITIONING.

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ABSTRACT

While dopamine (DA), particularly in the nucleus accumbens (NAC), was once assumed to mainly signal reward, more recent data suggest that the mesocorticolimbic DA system responds to a variety of salient and arousing events, including appetitive and aversive ones. Consistently, DA transmission has been shown to play a major role in aversively motivated emotional response, such as those established by classical fear conditioning. In classical fear conditioning, an emotionally neutral conditioned stimulus (CS), such as a tone, is paired with an aversive unconditioned stimulus (US), for example a footshock. As a result, the CS acquires aversive reinforcing properties and comes to elicit fear responses. The mesocorticolimbic DA system terminates in the medial prefrontal cortex (mPFC) and the NAC in addition to the amygdala. While the importance of the amygdala for formation and expression of conditioned fear has been firmly established, studies inactivating either the NAC or the mPFC have yielded the conclusion that these two structures are also involved in conditioned fear. Thus, it has been suggested that DA in these structures may modulate the formation and/or expression of conditioned fear.

The aim of the present thesis was to investigate the role of dopamine in the NAC, as well as in the mPFC, in classical fear conditioning. In a first series of studies, we assessed the effects of different behavioral (contextual versus discrete CS, latent inhibition of conditioned fear) and pharmacological (withdrawal from an escalating dose of amphetamine) conditions on conditioned fear and accompanying alterations of NAC DA measured by in vivo microdialysis. An automated measure of freezing behavior was used to index conditioned fear. Considering the anatomical differentiations within the NAC, the alterations of DA transmission in the NAC core and shell were always investigated separately. Conforming to the notion of a functional dissociation, our results indicated different alterations in shell and core DA transmission concomitant with a conditioned fear response. Additionally, we showed that increased or decreased expression of fear was accompanied by a decreased CS-evoked DA release in the shell of the NAC. It was proposed that these data are consistent with the notion that DA in the shell does not signal stimulus valence per se,
but may participate in signaling a change in stimulus valence. In the core, increased expression of fear were accompanied by an increased CS-evoked DA release. This suggests that DA in the core may reflect the direct impact of the CS on the behavioral response. A second series of experiments investigated the role of mPFC DA during conditioned fear. First, DA release in the mPFC was assessed by in vivo microdialysis during the potentiation of a conditioned fear response by previous treatment with an escalating-dose schedule of amphetamine. Second, we examined the effects of local microinfusions of a DA antagonist or agonist into the mPFC in a fear-conditioning experiment. The results indicated that a potentiation of DA release, possibly within a particular physiological range, was correlated with an increased fear response, while pharmacological DA receptor stimulation or blockade in the mPFC impaired the expression, but not formation, of conditioned fear. We suggested that an inverted U-shaped function may relate the expression of conditioned fear to DA receptor stimulation in the mPFC.

Together with the existing literature our data showed that NAC and prefrontal DA transmission participate in the organization of conditioned fear behavior. In the NAC, DA transmission may permit to modulate the allocation (conditioning) or re-allocation (expression) of the CS salience. Concerning the role of prefrontal DA in fear conditioning, it seems now clear that DA transmission in the mPFC plays a modulatory role mainly during the expression, but less during the formation. While it was previously also suggested that DA in the mPFC may support extinction, our finding with pharmacological manipulations of mPFC DA transmission demonstrated that DA transmission in the mPFC is essential for normal expression of conditioned fear.