Plasticity of the dopaminergic system: drug–stress cross-sensitization and fear conditioning

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Studies in laboratory animals indicate that pharmacological and environmental activations of mesocorticolimbic dopamine (DA) pathways can lead to long-lasting changes in their reactivity. To test for these effects in humans, we conducted positron emission tomography (PET) studies of (i) drug–stress cross-sensitization, and (ii) fear conditioning.

Study 1 used PET with [11C]raclopride to test whether a repeated intermittent psychostimulant regimen can sensitize the striatal DA response to stress. Seventeen healthy volunteers initially underwent two baseline PET scans during a low stress motor control task and the Montreal Imaging Stress Task (MIST). During the following week, they received three administrations of either D-amphetamine (0.3 mg/kg, p.o.) or placebo. Two weeks after the last drug administration (0 or 0.3 mg/kg), participants had a 2nd PET scan with the MIST. In subjects who had previously received D-amphetamine, the stress-induced striatal DA response was increased (p < 0.001), suggesting the development of drug–stress cross-sensitization.

In study 2, we used PET with [18F]fallypride to measure brain-wide DA release during the expression and inhibition of conditioned fear. Twelve healthy volunteers underwent a baseline PET scan, after which an electric shock was paired with a visual cue. During a 2nd PET scan, participants were exposed to the shock-paired cue. Finally, a 3rd PET scan was performed following a reversal learning procedure to study DA release during the inhibition of conditioned fear. A priori region-of-interest analyses identified a main effect of day (p = 0.04) in bilateral hippocampus reflecting increased DA release during the inhibition of conditioned fear, compared to the expression of conditioned fear (p = 0.028) and compared to baseline (p = 0.045). Brain-wide voxel-wise analyses also identified increased DA release in the left hippocampus during the inhibition of conditioned fear, compared to baseline (p < 0.001, uncorrected), and in the posterior cingulate gyrus, compared to the expression of conditioned fear (p < 0.001, uncorrected).

Together, these findings suggest that pharmacological and psychological events can modulate DA responses to stress and stress-related cues. These forms of dopaminergic plasticity may be involved in the development and maintenance of stressor-related disorders, such as post-traumatic stress disorder (PTSD), psychoses, and addictions.

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