S.25. Pharmacological enhancement of fear extinction in anxiety disorders: where do we stand?

S.25.01 Molecular mechanisms underlying emotional memories: importance to target fear

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Emotionally arousing and stressful experiences are remembered well in general. From the evolutionary point of view this is highly beneficial: it is important to acquire and remember important information which enables adaptation to comparable situations in the future. In some individuals however (intrusive) memories are vividly and inappropriately expressed, such as seen in post-traumatic stress disorder (PTSD). Unraveling the molecular and cellular mechanisms that underlie enhanced memory formation of stressful events is therefore highly relevant. Exposure to a stressor activates the hypothalamus-pituitary-adrenal (HPA)-axis which results in enhanced release of glucocorticoid hormones from the adrenal glands. These hormones, via activation of mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) regulate neuronal function and promote behavioral adaptation to stressful events. How they regulate emotional memory formation and promote behavioral adaptation remains elusive.

In this presentation we will show that corticosteroid hormones, via activation of GRs, regulate AMPA receptor mediated synaptic transmission and AMPA receptor mobility which are critical endpoints for memory formation. In addition, GRs target specific signaling pathways which regulate AMPA receptor function as well as emotional memory formation. Finally we will show that early life adversity – which programs the activation of the HPA-axis and is an important risk factor for the development of psychopathology and anxiety – determines synaptic function and enhances contextual fear later in life. The effects of early life adversity on contextual fear can be prevented by targeting glucocorticoid receptors.

S.25.02 Effects of MDMA on self-referent encoding and personal memories: implications for its use in PTSD

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3,4-methylenedioxymethamphetamine (MDMA) was initially called 'empathy' rather than 'ecstasy' as it was seen to promote openness and enhance social interaction. Preliminary research suggests that MDMA may boost the effectiveness of psychotherapy for post-traumatic stress disorder (PTSD). As psychotherapy for PTSD generally involves revisiting traumatic memories, we aimed to determine how MDMA affects encoding and retrieval of emotional memories. Effects of 100 mg of MDMA-HCl were compared with placebo in a double-blind, repeated-measures design. We used functional magnetic resonance imaging (fMRI) and self-referent encoding (SRE) of positive and negative adjectives in relation to oneself, or another person or a neutral condition. The placebo condition replicated typical SRE effects in behavioural and fMRI data. MDMA decreased recognition accuracy but did not influence the self-positivity bias even though ratings of compassion and euphoria showed marked MDMA-increases. A second task in the same study – recollection of each participant's favourite and worst autobiographical memories (AMs) – showed a significant effect of memory valence: hippocampal regions showed preferential activations to favourite memories and executive regions to worst memories. MDMA augmented activations to favourite memories in the bilateral fusiform gyrus and somatosensory cortex and attenuated activations to worst memories in the left anterior temporal cortex. Favourite memories were rated as significantly more vivid, emotionally intense and positive after MDMA than placebo and worst memories were rated as less negative. These findings are consistent with an MDMA-induced positive emotional-bias for autobiographical memories and suggest a potential mechanism through which MDMA might enhance the effectiveness of psychological therapies.

S.25.03 Cannabinoid and glutamatergic targets for improving the treatment of maladaptive memory in fear and addiction

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Maladaptive associative memory processes are centrally implicated in both anxiety and substance use disorders. These memories have proved largely resistant to remediation by extinction learning, with maladaptive responding resurfacing following extinction-based interventions. As such, methods for potentiating extinction or directly weakening maladaptive memories have important implications for treating both anxiety and addiction. Endocannabinoid and NMDA receptor-mediated glutamatergic signalling are implicated in memory consolidation and may present important drug targets for the enhancement of extinction. This talk presents data from human experimental medicine paradigms examining the phytocannabinoid Cannabidiol (CBD) and NMDA receptor partial agonist D-cycloserine (DCS) for enhancing extinction, with a focus on the diverse challenges posed in extinguishing fear and reward-based memories. CBD potentiates the consolidation of explicit fear memory extinction in a fear conditioning paradigm and reduces cigarette smoking when inhaled in an on-demand fashion in a pilot intervention study. In contrast, while DCS may be effective in potentiating fear exposure therapy [1], its efficacy in substance use disorders is limited. This disparity is partially attributable to the different learning histories and processes involved in maladaptive memory formation in anxiety and addiction. Considering this, I present preclinical meta-analytic [2] and early human evidence suggesting a more efficacious approach in addiction may be to weaken maladaptive memories while they are unstable prior to their reconsolidation. This approach could also be fruitful in the treatment of anxiety disorders either alone or in combination with existing behavioural therapies, however its true clinical potential remains to be assessed.

References

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