Panel

35. Cellular and Circuit Mechanisms of Anhedonia: Experiment-Based Targets for Intervention?

35.1 Aberrant Structural and Functional Circuit Maturation Underlies Anhedonia: Novel Findings Using Viral-Genetic Approaches and High-Resolution Neuro-Imaging in Experimental Systems

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Background: Anhedonia is considered to denote aberrant function of pleasure and reward circuits, yet its neurobiological basis is not fully understood. Anhedonia often presages depres-sion, schizophrenia and other emotional disorders, providing strong impetus to uncover its basis and test mechanistic preventative or mitigating interventions. We have identified several measures of anhedonia in both rats and mice that had experienced aberrant sensory signals (fragmented unpredictable sensory signals from maternal care; FRAG). Here we reasoned that disruption of cognate sensory input is known to distort the development of visual, auditory and motor circuits, and probed if disrupted maternal-derived sensory signals distort the maturation of the pleasure-reward circuit, promoting anhedonia

Methods: In mice, we employed viral-genetic tracing methods as well as immunohistochemistry to examine molecularly-defined pathways bridging nucleus accumbens (NAc) and amygdala in control and FRAG mice. We employed DREADD technology to probe the functions of pathways that differed in these groups. We used sucrose preference, estrous-female-scent and 3- chamber tests of anhedonia. In rats, we examined structural brain circuits using high-resolution diffusion tensor imaging (DTI) in FRAG and control cohorts, and cellular/regional activation was probed using cFos. We employed viral-genetic approaches to manipulate the expression of candidate genes. Finally, we tested for anhedonia using sucrose preference and social play.

Results: Several measures of FRAG-induced anhedonia were apparent in both mice and rats. Augmentation of CRH + -BLA-NAc pathways was found in FRAG mice compared to controls. In rats, DTI-tractography revealed increased structural connectivity of amygdala to medial prefrontal cortex in FRAG cohorts, as well as dispersion of DTI-apparent tracts between amygdala and NAc, indicating altered connectivity across fear/anxiety networks with pleasure/reward networks. Viral manipulation of these pathways reversed FRAG-induced anhedonia, suggesting that the long-term effects of early-life FRAG are modifiable in adulthood.

Conclusions: In experimental systems 'anhedonia' that follows disturbed patterns of sensory signals to the developing brain involves aberrant maturation of pleasure/reward circuits. Collaborative prospective studies in humans are examining the contribution of unpredictable and fragmented early-life environmental and maternal signals (in the context of other risk factors) to the emergence of anhedonia symptoms and employ MRI to assess the underlying circuit changes. Thus, the mechanistic insights provided by viral-genetic tracing and gene manipulations, feasible in experimental systems, should be immensely valuable to our understanding of human anhedonia a dimensional entity which is a core feature of several serious mental illnesses

Disclosure: Nothing to disclose.