American College of Neuropsychopharmacology

HOT TOPICS

Identifying novel mechanisms and treatment targets for irritability and aggression in psychiatric disorders

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Irritability, commonly defined as low threshold for anger, and its related constructs (anger attacks, hostility, and reactive aggression) are widely prevalent and disabling features of psychiatric disorders across the lifespan. We have previously shown that irritability improves with antidepressant treatment, and this improvement can independently (controlling for changes in overall depression severity) prognosticate longer-term clinical outcomes [1]. We have also shown that one in three adults with major depressive disorder exhibit elevated irritability which in turn is associated with elevated suicidal ideation [2].

Despite recognition of the clinical significance of irritability to the well-being of adults with psychiatric disorders, treatments remain limited. There is an urgent need to develop new treatments because commonly used medications are often ineffective and psychotherapy treatments are not always feasible or effective. Lack of preclinical models for irritability have served to limit the development of novel therapeutic approaches. A key knowledge gap for the field remains: How do we design ethologically valid translational experiments in animals and humans for irritability?

Animal models of pathological aggressive behaviors have helped inform the underlying neural circuit mechanisms and suggest that pathological aggression may represent increased activity of subcortical circuits that serve adaptive aggression and/or disruption of cortical inhibition over these aggression-related subcortical circuits [3]. Habenula, an evolutionarily conserved brain region that signals negative reward prediction error (i.e., value of a reward is less than expected), has emerged as a key region in modulating the valence of aggressive behaviors. Recently, Flanigan et al. demonstrated that afferent signaling from orexin neurons of lateral hypothalamus to GABAergic neurons of lateral habenula reduced habenular activity and promoted aggression [4]. Furthermore, systemic administration of drugs blocking orexin receptor type 2 (OX2R) reduced aggression [4]. However, development of selective OX2R antagonists may be limited by the uncertainties regarding how inter-male aggressive behavior in preclinical models relates to syndromic features of irritability.

As a field, we need to develop novel experimental paradigms for irritability in humans and their analogous preclinical models. While there are several human laboratory experiments of aggression [5], how responses to these tasks relate to syndromic features of irritability remains unclear. Furthermore, emotional, physiological, and behavioral states that are associated with irritability resemble the responses evoked by failure to receive an expected reward, or frustrative nonreward (FNR). To date, neuroimaging studies of FNR have been limited to pediatric samples [6]. While pediatric neuroimaging studies [6] have linked irritability to impaired reward processing, especially as it relates to FNR, it remains unclear whether irritability in adults has similar neural circuit mechanisms. Therefore, our group is systematically studying syndromic features of irritability in ongoing naturalistic cohort studies (ages 10–85 years) to identify novel targets for drug discovery using resting-state and FNR-task-based neuroimaging and detailed immunophenotyping approaches (multiplex assays, mass cytometry, and autoantibody arrays).

In conclusion, our work has underscored the public health burden of irritability and its related features. Recent preclinical studies and pediatric neuroimaging investigations have generated much enthusiasm in the field regarding development of novel therapies based on specific neural circuit mechanisms.

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ADDITIONAL INFORMATION

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