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RESEARCH HIGHLIGHT

Neuroscience targets and human studies: future translational efforts in the stress system

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Stress plays a role in the initiation, development, and reoccurrence of drinking during recovery from alcohol use disorder (AUD). The interplay between the stress and AUD could be mediated by multiple systems. Therefore, the exploration of these relationships should be evaluated as targets for developing AUD pharmacophores. The pharmacological research targeting the hypothalamic-pituitary-adrenal (HPA) axis has been very active in the last few decades, with the majority of efforts focused on the development of corticotropin releasing factor receptor 1 (CRF_1) antagonists. Unfortunately, CRF_1 antagonists, while showing promise in preclinical models, have not translated to humans [1].

The stress system is one of the most evolutionary conserved systems and designed to adapt to both stochastic and chronic insults in order to regulate homeostasis. To do this, it is interwoven with a neuroendocrine mechanism that regulates the autonomic nervous system. Given this interplay, broadly blocking one receptor (CRF_1) system-wide with a potent and highly selective CRF receptor antagonist that acts at the receptor CRF binding site may induce other compensatory mechanisms. As CRF-containing neurons and noradrenergic neuronal projections interact via the feed-forward loop, the narrow target of the CRF_1 blockade will become ineffective on a clinical outcome where there is lower noradrenergic activation (AUD patients in recovery in a supportive inpatient setting), compared to the preclinical models (animals exposed to or deprived of alcohol and housed in individual cages). Alternatively, developing allosteric modulators that do not act at the CRF binding site may provide a means to modulate the stress system and to fine-tune receptor signaling by acting at sites distinct from the orthosteric site to modify receptor signaling.

Given the complexity of the CRF system per se, other receptors (CRF_2), ligands (urocortin), and the associated binding protein (CRFBP) should also be evaluated in the development of new pharmacophores to target the stress system. It is important to note that interactions between components of the stress system occur and that G protein-coupled receptors like CRF_1 and CRF_2 can network with other proteins. Toward this end, there are studies developing negative allosteric modulators [2] that aim to specifically reduce the excitatory effect produced by an interaction between CRF, the CRF_2, and the CRFBP [3].

Approaches to better guide future endeavors should also include network-based paradigms that are conducted in parallel in both sexes across species. The intricate relationship between the stress pathways and other systems that regulate neuroactivation has taught us the importance of interfacing preclinical and clinical paradigms in parallel, rather than subsequent to one another (conventionally: preclinical first, clinical later) with a balanced sample that can account for sex as biological variable. In AUD research, there are both preclinical and clinical paradigms that are well-validated; Brain research in human studies, however, has been limited compared to the tools available in preclinical models, therefore, parallel brain investigations between rodents and humans are highly warranted.

A new report on pexacerfont [4], which examined imaging data from the original RCT [1], using seed-based analysis regions of interest (ROI), failed to show that there was a difference in the patients' blood-oxygen level dependent responses, while performing the Trier Social Stress Test (TSST). Furthermore, in the whole brain analysis, there was no effect of pexacerfont (or pexacerfont x stress interaction) on activation of any brain regions known to be disrupted by AUD. This study further demonstrated that despite substantial preclinical evidence of pexacerfont's brain permeability and efficacy, CRF_1 antagonists have failed to translate preclinical brain responses into the clinical setting [1]. The neuroimaging approach utilized in the authors' secondary analysis was well-planned as patients responded to the TSST and significant neuroactivation was observed regarding the drug condition; however, these data highlight the urgency to develop translational approaches that allow for parallel validation of preclinical and clinical studies in the investigation of brain responses.

Incorporating neuroimaging and functional task-based connectivity analysis in the development of medications to treat AUD has shown value in the alcohol research field. In addition, resting state functional connectivity offers a more complex, holistic picture of the circuits involved in comparison to a single ROI, which can be beneficial in evaluating the complexity of the stress pathway and its interaction with other systems. Moreover, the rodent's anteroposterior networks are anatomically homologous to the human salience (SN) and default-mode (DMN) [5] network. Rodents' functional magnetic resonance imaging signals in the DMN-like network display spontaneous anti-correlation with anterior-parietal brain areas, which are consistent with human resting state functional connectivity (a measure of emotional regulation).

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The DMN divergent resting state functional connectivity with the SN may contribute to increase attention to alcohol cues, increased withdrawal, craving, and stress-induced drug reoccurrence in humans; therefore, disruption in the DMN resting sate functional connectivity in preclinical models may serve as a biomarker to assess responses to pharmacological treatments. Of note, specifically for the investigation of the stress system, the DMN is also a hub for other neurotransmitters associated with addiction, making the aberration in the DMN a target to evaluate the extensive interconnection of the stress system with specific mechanisms associated with AUD endophenotype. However, network-based analysis approaches (particularly task-based) have not been conducted in parallel in human and animal studies, making translational success in psychiatric disorders and drug responses unpredictable.

Interspecies parallel rodent/human paradigms focused on network level-changes offer compelling novel approaches. With that being said, the harmonization of central and peripheral variables is still a limitation. Translational studies should assess critical functional domains in both species to advance mechanistic understanding of interspecies neural network components involved in the AUD process. Moreover, when combined with neuroimaging, the use of selective pharmacophores has the same degree of saliency across species and offers the opportunity to identify and spatially resolve the neural circuits underlying acute stress activations. As AUD involves complex neural relationships between diverse functional domains, a parallel human/rat network-level approach has the potential to reduce the translational gaps between clinical and preclinical studies and provide a biomarker for drug response. Importantly, this interspecies approach will increase the opportunity to evaluate relationships between peripheral and central activity which is very challenging to incorporate in human studies.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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