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"Hierarchy Dependent Social Behavior During Systemic Inflammation"

By

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Cell Biology, Neuroscience and Physiology Program
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Rollins College

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Friday, November 7th, 2025
Cancer Center, G1196
1:00 P.M.

Join Zoom presentation

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ABSTRACT

Infections and other forms of systemic inflammation lead to substantial but inconsistent changes in social behavior, ranging from social withdrawal that limits pathogen spread, to seeking out social support. The underlying factors leading to variable social responses during inflammation remain unknown. Social hierarchies established within group-living animals contribute significantly to inter-individual variability in physiology and behavior. This thesis examines how social hierarchy affects social behavioral outcomes and neural activity during systemic inflammation.

We treated male and female mice with systemic administration of the bacterial endotoxin lipopolysaccharide (LPS) and subsequently evaluated social behavioral responses to inflammation. First, we tested investigation of immobilized novel and cagemate conspecifics in a social novelty test. We find that sick dominant male mice prefer familiar cagemates over novel conspecifics, reversing the novelty preference observed in healthy controls. Conversely, sickness does not change social preference in subordinate males and in female mice of either rank. In the same task, females and subordinate males have increased orientation toward social targets during sickness. Secondly, we used a multidimensionality reduction approach to identify rank-specific responses to LPS-treatment in a naturalistic direct social interaction task. We find distinct signatures for each rank-treatment combination, confirming hierarchy-dependent social interactions during systemic inflammation. Brain-wide immediate early gene mapping of the LPS responsive interoceptive brain network revealed rank-dependent changes. We found that LPS increases c-fos expression in the central amygdala and the bed nucleus of stria terminalis of dominant mice. Within the central amygdala, rank differences emerged specifically in the medial subdivision. Upstream, in the central capsular subdivision, we found that oxytocin receptor-expressing (CeA-OTR+) neurons constituted 40-60% of LPS-activated cells. Moreover, in dominant mice we detected increased c-fos expression in PVN oxytocin neurons. Using monosynaptic retrograde tracing, we identified direct projections from LPS-c-fos expressing PVN neurons and from PVN oxytocin neurons to CeA-OTR+ cells. These findings suggest that LPS-treatment targets the brain oxytocinergic system in a rank-dependent manner to gate CeA output. In vivo fiber photometry recordings revealed that CeA-OTR+ neurons encode proximity and orientation to novel conspecifics in males but not females, with preliminary evidence that LPS disrupts this encoding. While optogenetic suppression of CeA-OTR+ neurons altered social preferences in healthy mice, future work is needed to resolve a causal role in hierarchy-dependent sickness behavior.

Taken together, our work demonstrates that social hierarchy has a major impact on sickness-induced adaptations in social behavior, and indicates that oxytocinergic modulation of the central amygdala could represent a substrate for hierarchy-dependent responses to systemic inflammation.