Maj Institute of Pharmacology
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Title of PhD thesis:

***Reward sensitivity, social motivation and endogenous opioid signaling in adolescent C57BL/6 mice***

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# Abstract

Social behaviors improve access to essential resources, reduce vulnerability to threats, and provide reproductive opportunities. They are inherently rewarding, and the motivational value of social interactions changes across adolescence, likely reflecting the maturation of neural systems regulating reward, learning, and stress. Here, I investigated the rewarding effects of social contact in a non-reproductive context in early (pubertal onset), mid (peripubertal), and late (sexual maturation) adolescent C57BL/6 mice. I show that changes in endogenous opioid signaling may be a key mechanism shaping the maturation of social behavior.

First, I assessed prosocial behavior, affective state discrimination, and social conditioned place preference (CPP) in adult mice. Females were significantly more likely to perform prosocial choices than males. However, sex had no effect on the ability to discriminate the familiar conspecific with a changed affective state, or on preference for a context associated with sibling social housing. Adult mice were highly responsive to social cues, establishing a robust model for examining the neural mechanisms of social motivation.

Next, I examined how adolescence shaped sensitivity to the rewarding effects of social interaction. Both male and female adolescent mice displayed a lower preference for a context associated with social housing than adults. Adolescents also showed diminished palatable food CPP, suggesting a general decrease in natural reward preference, while sensitivity to cocaine was comparable to that of adults. When data across all reward types were analyzed together, adolescence was consistently associated with lower overall CPP expression, challenging the view of adolescence as a period of increased reward sensitivity.

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Previous work has pointed to endogenous opioid signaling as a critical modulator of social behavior. I analyzed developmental changes in the expression of genes encoding opioid receptors and peptides. Across adolescence, prodynorphin (*Pdyn*) expression decreased in the medial prefrontal cortex and dorsal striatum, while the proportion of cells co-expressing *Pdyn* with somatostatin mRNA in the medial prefrontal cortex, or with κ opioid receptor (KOR) mRNA in the dorsal striatum and nucleus accumbens, increased.

To test whether these developmental shifts in basal *Pdyn* expression are associated with behavioral changes, I assessed social and cocaine CPP following pharmacological or genetic inhibition of KOR function. Administration of the long-acting KOR antagonist - norbinaltorphimine, as well as complete *Pdyn* gene inactivation, selectively reduced social, but not cocaine CPP, only in late adolescence. These findings suggest that social motivation undergoes qualitative changes across adolescence, with younger stages less dependent on stress-sensitive circuits and more mature stages increasingly recruiting stress-modulating dynorphin/KOR pathways.

By integrating behavioral, genetic, and pharmacological evidence, my work demonstrates how the dynorphin/KOR system contributes to the maturation of social reward in non-reproductive contexts. I provide the first characterization of adolescent reorganization of opioid gene expression in the medial prefrontal cortex and striatum, revealing age-dependent refinements in dynorphin-expressing neuronal populations. These findings advance current knowledge by suggesting that developmental refinement of the dynorphin/KOR system may increase the role of relief from isolation in peer social drive, offering a potential link between adolescent social motivation and stress-sensitive neural circuits.

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