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The MCH System and Emotional-Like Behavior

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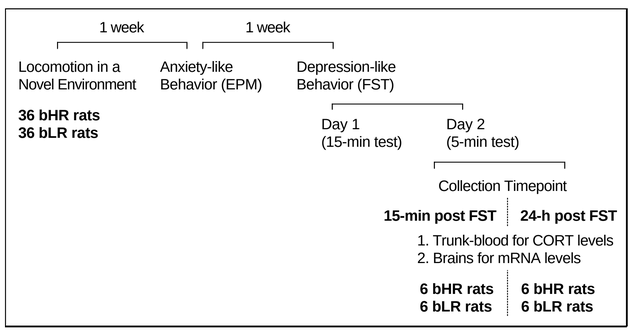
INTRODUCTION

The melanin-concentrating hormone (MCH) is a neuropeptide that exhibits some of the hallmarks of a regulator of affective states [1-2]. Reliable animal models of depression are crucial to the success of understanding the molecular mechanisms underlying depressive disorder and therefore improve treatment options. Among the different approaches described to construct a good animal model, selective breeding for divergence in novelty-seeking traits (bHR, bred High-Responder; bLR, bred Low-Responder) correlates with stress-reactivity, spontaneous anxiety-like behaviors and other measures of "emotionality" [3]. Moreover, novelty-seeking behavior has recently been shown to predict vulnerability in a rodent model of depression [4]. Therefore, identifying genetic factors that may account for such vulnerability are key determinants not only for the illness outcome but also to develop better-tailored treatment options. The aim of this study was to ascertain the role of the MCH system in the propensity to develop mood disorders (i.e., basal differences in bHR vs. bLR rats).

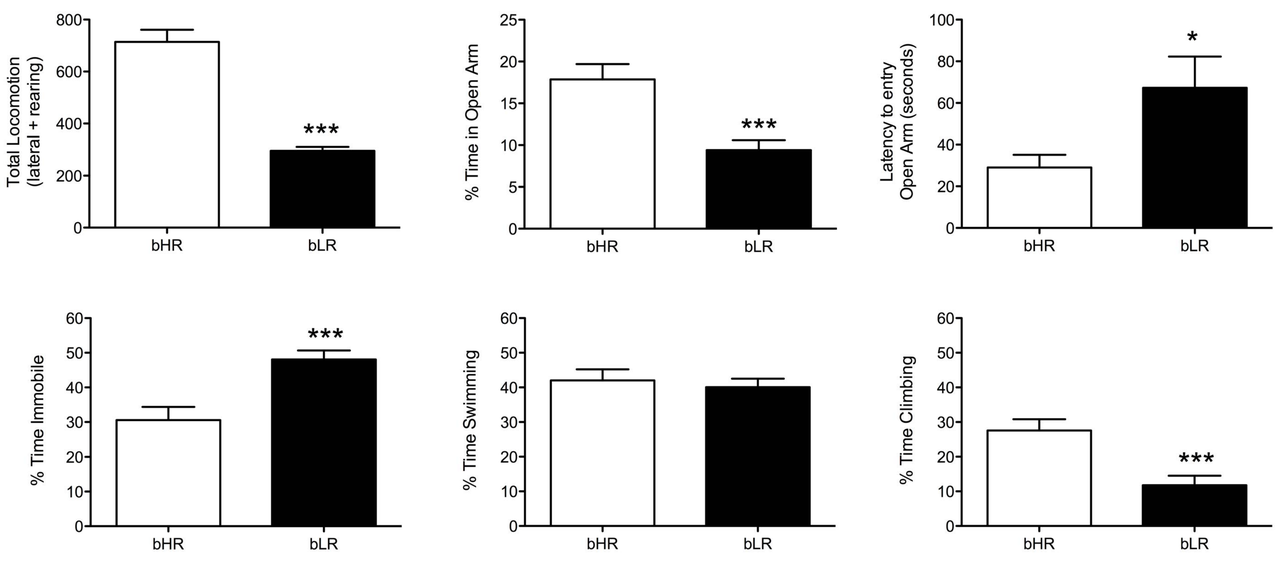
EXPERIMENTAL DESIGN



Experimental Design: bLR and bHR rats from the 9th generation of the breeding colony (University of Michigan) were screened for several behavioral testing: (a) novelty-seeking behavior (locomotor activity in a novel environment); (b) anxiety-like behavior (elevated-plus maze, EPM); (c) depression-like behavior (forced-swim test, FST: Day 1, 15-min and Day 2, 5-min test). Rats were killed 15-min or 24-h after Day 2 FST session, their brains removed and fast frozen. Trunk-blood was collected for plasma corticosterone (CORT) measurements. Rats were sorted based on immobility performance in the FST (measure of depression-like behavior) and a subset of 6-bLR and 6-bHR rats from each collection time-point were selected for molecular analyses. Gene expression analysis was performed by *in situ* hybridization for pMCH (hypothalamus) and MCH1R (PFC, NAc-Shell, amygdala, CA1).

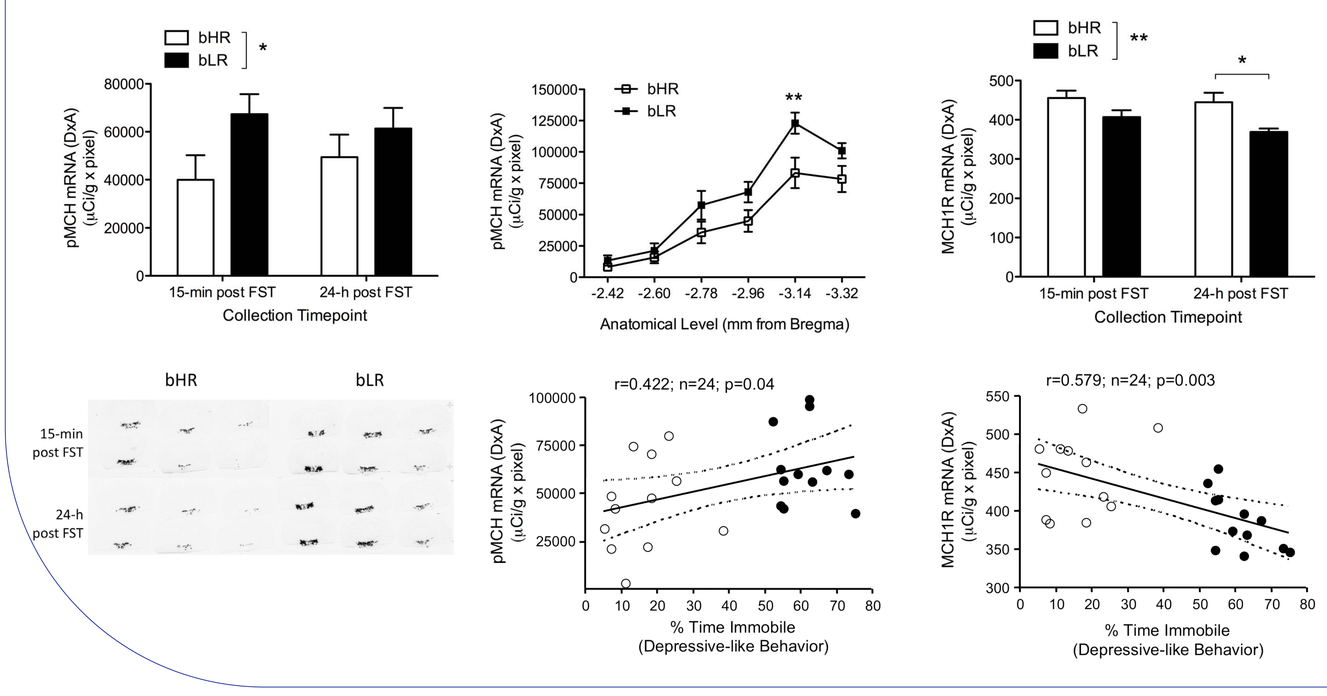
RESULTS

1. Behavioral Phenotype: bHR vs. bLR Rats



- bLR rats were less active in a novel environment than bHR rats ($p<0.0001$).
- Consistent with an increase in anxiety-like behavior, bLR rats spent less time in the open arm ($p<0.001$) and a greater latency to enter the open arms of the maze compared with bHR rats ($p<0.05$).
- bLRs rats spent more time immobile ($p<0.001$) and less time active (climbing behavior, $p<0.001$) than bHR rats, as it was expected for an increased depression-like behavior.
- There was no difference between bLR and bHR rats in CORT levels 15-min or 24-h after FST (data not shown).

2. *In Situ* Hybridization Analysis: The MCH System



- Independently of the collection time-point, bLR rats showed a 44% increase in hypothalamic pMCH mRNA ($p<0.05$) when compared to bHR rats. Changes in pMCH mRNA mainly occurred at the posterior level of the hypothalamus (-3.14 mm from Bregma, $p<0.01$).
- bLR rats showed a 14% decrease in hippocampal CA1 MCH1R mRNA ($p<0.01$) when compared to bHR rats. There was no change in MCH1R mRNA levels in the other brain regions analyzed (PFC, NAc-Shell, amygdala).
- Immobility time in the FST (depressive-like behavior) correlated positively with the amount of hypothalamic pMCH and negatively with that of hippocampal CA1 MCH1R.

CONCLUSIONS

The results indicate that the bLR-bHR is a useful rat model to investigate individual basal genetic differences that participate in the propensity to manifest differences in emotional responsiveness (i.e., depression- and anxiety-like behaviors). They also point to the MCH system (i.e., chronically higher pMCH release and consequently receptor down-regulation) as a candidate biomarker for the severity of depressive-like behavior. The data indicate that MCH1R participates in the modulation of depression-like behavior through a process that involves the CA1 region of the hippocampus, supporting the possible use of MCH1R antagonists in the treatment of depression.

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