

## THE EFFECTS OF ACUTE PSYCHOLOGICAL STRESS ON ENZYMES REGULATING THE KYNURENINE PATHWAY

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### INTRODUCTION

An emerging body of literature recognizes the relationship between stress and inflammation. The kynurenine pathway is particularly relevant because it accounts for the majority of tryptophan's metabolism [1]. Activation of the kynurenine pathway depletes the tryptophan pool for serotonin, and has been associated with the emergence of depressive-like symptoms and "sickness behaviour" (anhedonia, anxiety, and sleep disturbances) in animals [1]. The first and rate limiting step of the kynurenine pathway converts tryptophan to kynurenine and can be catalyzed by tryptophan 2,3-dioxygenase (TDO), which operates under basal conditions, or by indoleamine 2,3-dioxygenase 1 (IDO1), which predominates under inflammatory states [2]. Indeed, previous research has shown that IDO1 can be induced by cytokines, such as tumor necrosis factor alpha (TNF $\alpha$ ) [1,2]. Recent data from our lab indicates that TNF $\alpha$  protein is increased in the amygdala 4 h after exposure to an acute stressor. Hence, this investigation attempted to determine the effects of acute stress on mRNA levels of enzymes regulating the kynurenine pathway.

### METHODS

Adult, male, Sprague Dawley rats ( $N=48$ ) were subjected to 120 minutes of restraint stress and rapidly decapitated 1 h, 2 h, 4 h, 6 h, or 24 h later. Trunk blood was collected and analyzed for circulating corticosterone and TNF $\alpha$  levels. Brains were extracted and excised into amygdalae, hypothalami, prefrontal cortices, and hippocampi. RNA was isolated, followed by cDNA synthesis, and quantitative PCR (qPCR) to quantify mRNA levels of IDO1, TDO, kynurenine aminotransferase 1 (KAT1), kynurenine 3-monooxygenase (KYNM), kynureninase (KYNU), and 3-hydroxyanthranilate 3,4-dioxygenase.

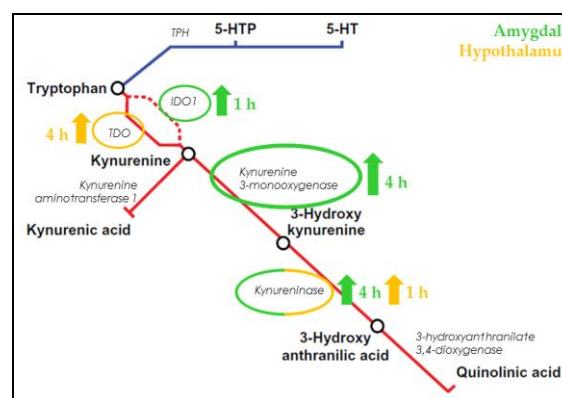
### RESULTS

Results indicated that plasma corticosterone levels were elevated 2 h after the acute stressor, while circulating levels of TNF $\alpha$  were increased at the 1 h and the 2 h post stress time points. Analysis of amygdalar qPCR data indicated an upregulation of IDO1 mRNA at the 1 h time point, and increased KYNM and KYNU mRNA at the 4 h time point.

There were no amygdalar mRNA changes in the other genes. Regarding hypothalamic data, there was an increase in TDO mRNA at the 4 h time point and KYNU mRNA at the 1 h time point. These results are summarized in Figure 1.

### DISCUSSION AND CONCLUSIONS

Increases in expression of kynurenine pathway enzymes in the amygdala occurred in a time dependent manner. Taken together, the data is concordant with previous reports, which indicate that IDO1 and TDO can be induced by TNF $\alpha$  and corticosterone, respectively [1,2]. The result of increased amygdalar KYNM and KYNU mRNA following acute stress represents a novel finding and suggests that stress shifts the kynurenine pathway towards neurotoxic metabolites, such as 3-hydroxykynurenine and quinolinic acid, which may aggravate the symptoms of inflammation-induced depression. Follow up work on this study would investigate mRNA changes in other brain regions, such as the prefrontal cortex and the hippocampus. In addition, plasma and brain concentrations of tryptophan, kynurenine, kynurenic acid, and quinolinic acid would be determined to see if they are in accordance with the mRNA data. Ultimately, the present study highlights the kynurenine pathway as a potential therapeutic target for inflammation-induced depression.



**Figure 1.** Enzymes and metabolites of the kynurenine pathway along with the results obtained in this experiment.

### REFERENCES

1. Dantzer R, et al. *Nat Rev Neurosci.* 9:46-56, 2010.
2. Kiank C, et al. *PLoS ONE.* 5:e11825, 2010.