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Neurobiological Insights into the Chronic Mild Stress (CMS) Model of Depression: Sex Differences in Serotonergic Neurotransmission

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S u m m a r y: Chronic mild stress (CMS) was developed in the late 1980s and is one of the most extensively investigated animal models of depression to-date. Research from our lab has underlined the importance of serotonin in the manifestation of sexually dimorphic neurochemical, behavioural and immune responses. Novel data reveal that both CMS application and chronic antidepressant treatment modulate hippocampal serotonergic 1A (5-HT$_{1A}$) receptor mRNA levels in a sexually dimorphic manner.

INTRODUCTION

Major depression affects both sexes, but more women than men are likely to be diagnosed with depression in any given year. This sex-dependent differentiation has been largely attributed to the pronounced sex differences that predominate in both the anatomy and function of the human brain, as well as to the sexually dimorphic hormonal *milieu.* Chronic mild stress (CMS) was developed in the late 1980s and is one of the most extensively investigated animal models of depression to-date. In our initial studies in male rats exposed to a CMS regimen, we observed a decrease in the prefrontocortical serotonergic activity accompanied by an increase in hippocampal serotonergic activity; all alterations were reversed by chronic *imipramine* treatment [1]. In further comparative studies between male and female rats, we used a milder CMS protocol, which did not induce neurochemical alterations in male rats, but resulted in a significant decrease in hippocampal serotonergic activity in females [2]. Accordingly, exposure to CMS induces a wide spectrum of relevant neurobiological alterations in specific brain regions implicated in the pathophysiology of major depression. For instance, it has previously been reported that hippocampal serotonergic 1A (5-HT$_{1A}$) receptors are increased by CMS in male rats [3]. Given the prominent role of the hippocampus in the sex-dependent processing of stressful stimuli, in the present study we investigated whether sex differences exist in the expression of hippocampal 5-HT$_{1A}$ receptor upon CMS application and chronic antidepressant treatment.

METHODS

Male and female *Sprague–Dawley* rats, weighing 200-300 g, were used throughout this study and were either subjected to CMS and chronic antidepressant regimens or served as controls, as previously described [4]. At 24 h following the cessation of stressors/drug administrations, CMS-treated and control rats of both sexes were decapitated and their brains were processed accordingly for the immunohistochemical detection of digoxygenin (DIG)-labelled 5-HT$_{1A}$ riboprobes in the region of the hippocampus.

RESULTS

CMS application resulted in increased 5-HT$_{1A}$ mRNA levels in the CA1 and CA3 regions of the hippocampus in males but not in female rats. On

the other hand, 5-HT_{1A} mRNA levels in the CA1 region were induced in male but decreased in female controls upon chronic antidepressant treatment.

DISCUSSION

These novel data reveal that both chronic stress and antidepressant treatment induce sexually dimorphic effects on 5-HT1A receptor mRNA expression in the CA1 and CA3 regions of the hippocampus and lend further support to the prominent role of the hippocampal serotonergic system in the manifestation of sexually dimorphic responses in the CMS model of depression.

REFERENCES

1. Bekris S., Antoniou K., Daskas S., Papadopoulou-Daifoti Z.: Behavioural and neurochemical effects induced by chronic mild stress applied to two different rat strains. *Behav. Brain Res. 161*: 45-59 (2005)
2. Dalla C., Antoniou K., Drossopoulou G., *et al.*: Chronic mild stress impact: Are females more vulnerable? *Neuroscience 135:* 703-714 (2005)
3. Papp M., Klimek V., Willner P.: Effects of imipramine on serotonergic and beta-adrenergic receptor binding in a realistic animal model of depression. *Psychopharmacology (Berl) 114*: 309-314 (1994)
4. Pitychoutis P.M., Griva E., Ioannou K., Tsitsilonis O.E., Papadopoulou-Daifoti Z.: Chronic antidepressant treatment exerts sexually dimorphic immunomodulatory effects in an experimental model of major depression: Do females lack an advantage? *Int. J. Neuropsychopharmacol 12*: 1157-1163 (2009)