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Effect of chronic stress and antidepressant treatment on rat brain mitochondrial reactive oxygen species (ROS) production

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Hypercortisolism is known to underlie depressive illness; in fact depression is thought to be a behavioural representation of activated primary mediators of the stress response (Conti *et al.*, 2004). Therefore over the years a number studies have sought to learn the effect of antidepressant treatment on serum corticosterone profile. This study aimed to take this a step further and explore the relationship between serum corticosterone, antidepressants and mitochondrial function.

Treatments lasted 14 days using a 2x2 factorial design, where animals received 10mg kg^{-1} fluoxetine or 10mg kg^{-1} imipramine, intra-peritoneally, once a day at approximately 10:30am. Control animals were injected with vehicle. Concurrently animals received corticosterone (CORT; 5mg L^{-1}) or its vehicle ethanol (EtOH; 0.5% vv^{-1}) orally through drinking water.

Trunk blood was collected at the end of the 14 day period. Forebrain mitochondria were isolated as previously described (Markham *et al*., 2004). Serum corticosterone concentration was determined using a quantitative enzyme immunoassay. Reactive oxygen species (ROS) production was measured fluorometrically as described previously (Markham *et al*., 2008).

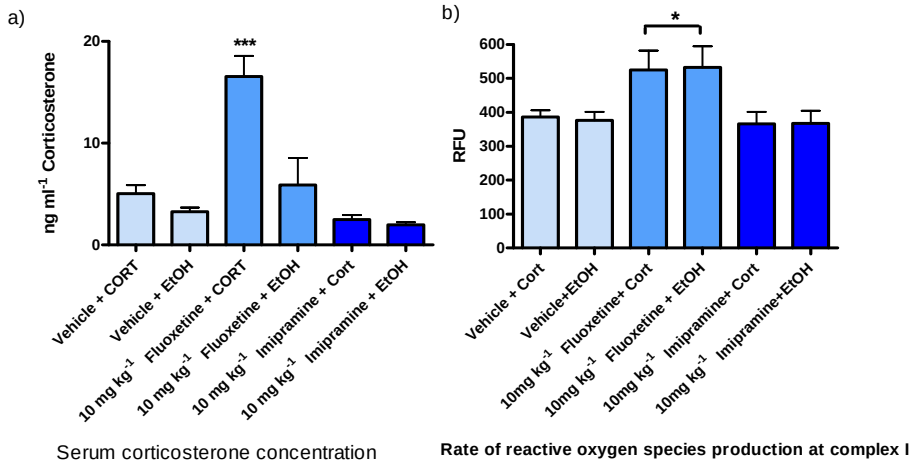

Figure 1 *The effect of antidepressants and oral corticosterone on a) circulating serum CORT and b) mitochondrial ROS production, expressed as relative fluorescence units. The data were analysed using one-way ANOVA followed by Tukey's post-test. Bars represent mean ± s.e.m.; n=3; *P<0.05 and ***P<0.001, compared to rest.*

Animals receiving fluoxetine in combination with oral corticosterone had significantly (P<0.001) higher concentrations of serum corticosterone, compared to all other groups. Additionally, fluoxetine treated

animals had a significantly ($P<0.05$) higher rate of ROS production, regardless of whether they received oral CORT or EtOH, compared to those treated with imipramine and control animals. This effect was specific to complex I supported respiration.

The decrease in serum corticosterone after treatment with imipramine is a part of the mechanism of action of this drug. Imipramine corrects the suppression of the HPA feedback loop that is associated with stress (Piwowarska *et al.,* 2009). While the increased levels of circulating serum corticosterone following fluoxetine injections can be explained by the ability of fluoxetine to act as an inducer of serum corticosterone for up to 2 h after administration (Yirimia *et al.,* 2001). Therefore, the timing of sample collection is critical in chronic studies. This study is unique in that no one has previously studied or shown the effect of concurrent *in vivo* treatment with antidepressants and corticosterone on rat brain mitochondrial ROS production.

Conti *et al.,* (2004) *J. Nuerosci.* 24(8), 1967-1975

Markham *et al.,* (2004). Eur. J. Neurosci. 20, 1189-119

Markham *et al.,* (2008) *Proc. B.P.S.* 5(2)-053P at http://www.pA2online.org/abstracts/Vol5Issue2abst053P.pdf

Piwowarska *et al., (*2009) *Pharmacol. Reports,* 61, 604-611

Yirimia *et al.,* (2001) *Neuro. Psych. Pharam.* 24 (5), 531-544