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# Reprint of: Contrasting effects of vortioxetine and paroxetine on pineal gland biochemistry in a tryptophan-depletion model of depression in female rats☆

Franklin M.[a,*], Hlavacova N.[b], Li Y.[c], Bermudez I.[a], Csanova A.[b], Sanchez C.[c], Jezova D.[b]

[a] Department of Biology and Biomedical Sciences, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK
[b] Institute of Experimental Endocrinology, Biomedical Research Centre of the Slovak, Academy of Sciences, Bratislava, Slovakia
[c] Lundbeck Research USA, Department of Biological Research, Paramus, NJ, USA

## ABSTRACT

We studied the effects of the multi-modal antidepressant, vortioxetine and the SSRI, paroxetine on pineal melatonin and monoamine synthesis in a sub-chronic tryptophan (TRP) depletion model of depression based on a low TRP diet.

Female Sprague-Dawley rats were randomised to groups a) control, b) low TRP diet, c) low TRP diet + paroxetine and d) low TRP diet + vortioxetine. Vortioxetine was administered via the diet (0.76 mg/kg of food weight) and paroxetine via drinking water (10 mg/kg/day) for 14 days.

Both drugs resulted in SERT occupancies > 90%. Vortioxetine significantly reversed TRP depletion-induced reductions of pineal melatonin and serotonin (5-HT) and significantly increased pineal noradrenaline NA. Paroxetine did none of these things.

Other studies suggest pineal melatonin synthesis may involve *N*-methyl-D-aspartate (NMDA) receptors and glutamatergic modulation. Here observed changes may be mediated via vortioxetine's strong 5-HT reuptake blocking action together with possible additional effects on glutamate neurotransmission in the pineal via NMDA receptor-modulation and possibly with added impetus from increased NA output.

## 1. Introduction

Depression is often comorbid with general medical conditions such as cardiovascular disease and diabetes. Likewise it has been associated with disruption of sleep and the hypothalamic-pituitary-adrenocortical axis (HPA). Enhanced hormone secretion from the HPA occurs in patients with depression and has been associated with the severity of depression symptoms and cognitive dysfunction (Murck et al., 2012; Belvederi Murri et al., 2016).

Sleep is essential for emotional and physical well-being and poor quality sleep for long periods of time increases the risk of depression. Dysfunction of endogenous melatonin secretion is associated with mood disorders. Patients with severe depression exhibit desynchronised and reduced melatonin secretion, in parallel with marked sleep disturbances (Pandi-Perunal et al., 2009). Melatonin is synthesised in the pineal gland during darkness periods and governs circadian and seasonal biological rhythms.

The pre-cursors of melatonin are TRP and then serotonin (5-hydroxytryptamine, 5-HT). During darkness the enzyme arylalkylamine *N*-acetyltransferase (NAT) is activated and converts 5-HT to *N*-acetyl serotonin which then undergoes further metabolism by the final enzyme in the pathway, 0-methyltransferase to melatonin. Physiologically, melatonin is involved in the regulation of the circadian cycle of core body temperature and hormones of the HPA axis. The sleep-wake cycle and motor activity can be disrupted in mice genetically depleted of 5-HT (Solarewicz et al., 2015). The release of melatonin from pinealocytes is stimulated by noradrenaline (NA). Another neurotransmitter involved is glutamate. Glutamatergic modulation of melatonin synthesis is known and more probably involves the interaction between the main cells of the pineal gland, pinealocytes and astrocytes (Villela et al., 2013). NMDA receptors have been observed in both of these pineal cells and are involved with the modulation of

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* Corresponding author.
*E-mail address:* mfranklin@brookes.ac.uk (M. Franklin).

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melatonin synthesis through such cell interactions (Kaur et al., 2005). Pineal melatonin content may be a sensitive measure of antidepressant activity similarly to NA and 5-HT as demonstrated in our previous studies with venlafaxine (Franklin et al., 1998).

Acute depletion of TRP reduces melatonin synthesis in healthy human volunteers (Zimmermann et al., 1993). In our previous study, pineal melatonin and 5-HT contents were decreased in an animal model of SSRI resistant depression based on sub-chronic TRP depletion in female rats (Franklin et al., 2015a,b). Over the periods 4–14 days of TRP depletion, pineal NA was generally unchanged. Significant correlations between pineal melatonin and corticosterone underpin our assumption that sleep quality may have been disrupted in TRP depleted animals (Franklin et al., 2015b).

Vortioxetine is a new antidepressant that inhibits 5-HT transporter (SERT) and is a 5-$HT_{1A}$ receptor agonist, 5-$HT_{1B}$ receptor partial agonist and a 5-$HT_{1D}$, 5-$HT_3$ and 5-$HT_7$ receptor antagonist and demonstrates cognition enhancing properties (Mork et al., 2013; Sanchez et al., 2015). In rat micro-dialysis studies it has been shown that vortioxetine dose-dependently increases extracellular 5-HT, NA, dopamine, acetylcholine and histamine in the cortex (Pehrson et al., 2012).

We have already published data from the greater part of this study with vortioxetine elsewhere (Hlavacova et al., in press). The aim of the second and separate part of the same study which is presented here is to investigate the possible antidepressant actions of vortioxetine and compare them to those of the SSRI, paroxetine on pineal gland biochemistry in female rats depleted of TRP. Comparison is made here using a clinically relevant and comparable level of brain SERT occupancy. For this report we have used sample materials from the aforementioned study (Hlavacova et al., in press).

## 2. Methods

### 2.1. Animals and study design

A depression-like state was induced by TRP depletion based on low TRP diet in female Sprague-Dawley rats as described elsewhere (Hlavacova et al., in press). They were randomly assigned into groups (n = 12/group) and placed on a 1) control diet (0.2% TRP), 2) low TRP diet (0.04% TRP), 3) low TRP diet plus paroxetine (administered via the drinking water at 10 mg/kg/day or 4) low TRP diet plus vortioxetine (0.76 g of vortioxetine per 1 kg of powdered low TRP diet, a dose shown to fully occupy SERT (Li et al., 2013). Animals were acclimatised to housing facilities for 8 days prior to testing. They were kept in a temperature controlled room (22 °C ± 2 °C) under a 12:12 h light/dark cycle (lights on at 06:00 a.m.). Animals were grouped 2 per cage with free access to food and water. All animal groups were studies simultaneously. All animal procedures were performed in the morning and were approved by the Animal Health and Animal Welfare Division of State Veterinary and Food Administration of the Slovak Republic and conformed to the NIH Guidelines for Care and Use of Laboratory Animals as for previous studies with vortioxetine. A more in depth account of the study design is published elsewhere (Hlavacova et al., in press).

Effects on procedures carried out in TRP depleted female rats may be influenced by the time of their estrous cycle (Jans et al., 2007). Proestrous/estrus events tend to be dictated by lighting times, but under normal lighting schedules (as in the present study) tend to occur during the late afternoon to early hours of the morning (Witcher and Freeman, 1985). Hence, all animal procedures were performed in the morning (usually (08.00–11.00 h) to reduce estrous cycle effects. Serum estradiol concentrations were measured to take account of possible differences in the estrous cycle.

### 2.2. Drugs

Vortioxetine hydrobromide was supplied by Lundbeck Research USA (Paramus, NJ, USA). Paroxetine hydrochloride was purchased from Sigma-Aldrich, St Louis, MO, USA.

### 2.3. Blood and organ collection

Following the end of procedures rats were quickly moved to an adjacent room and euthanized by decapitation. Trunk blood was collected into polyethylene tubes without anticoagulant. The clotted blood was spun at 3000 rpm for 15 min at 4 °C and the serum was separated. The brain and pineal gland were quickly removed from the skull. Tissues were dissected out as necessary on an ice-cold plate and frozen in liquid nitrogen. Tissues were placed into plastic cryo-tubes. Serum aliquots and tissue samples were placed in storage at − 80 °C until required for analysis.

### 2.4. Biochemistry

Pineal 5-HT and NA content was measured by HPLC with electrochemical end-point detection (Chi et al., 1999). Melatonin was measured by an in-house direct radioimmunoassay (RIA) with utilisation of 125I as ligand and the inter-assay and intra-assay coefficients of variation (CV) were < 6% (Fraser et al., 1983).

### 2.5. Statistics

Data was analysed by the Kruskal-Wallis test and post hoc by the Mann Whitney test. Results are expressed as mean ± SEM values. Overall level of significance was defined as $p < 0.05$.

## 3. Results

A significant main effect of group was observed for pineal melatonin (KW = 12.9; $p < 0.005$). Melatonin was significantly decreased in TRP depleted versus control animals ($p = 0.01$). Vortioxetine treatment significantly reversed this trend ($p = 0.01$) but paroxetine did not (Fig. 1).

A significant main effect of group was observed for pineal 5-HT (KW = 17.7; $p < 0.001$). Pineal 5-HT was significantly reduced in all TRP depleted animals as compared to those in the control group (Fig. 2). This trend was significantly reversed by vortioxetine ($p = 0.04$) but not by paroxetine treatment.

No significant effect of group was shown for pineal NA content (KW = 4.9; $p = 0.18$; see Fig. 3), although vortioxetine treatment did demonstrate an increased trend-effect versus all other groups.

## 4. Discussion

Findings which are fully reported elsewhere showed that all TRP

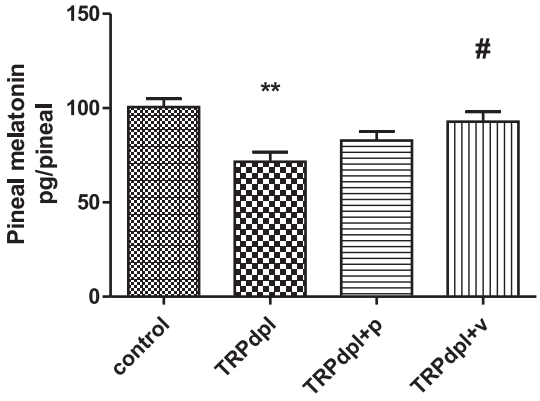


**Fig. 1.** The effect of vortioxetine (v) and paroxetine (p) on pineal melatonin content. Results are expressed as means ± SEM. #$p < 0.05$, **$p < 0.01$. #versus TRPdpl; *versus control.

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