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Letter to the Editor

Clomipramine and Glucocorticoid Receptor Function

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In response to Carvalho LA, Juruena MF, Papadopoulos AS, Poon L, Kerwin R, Cleare AJ, Pariante CM. Clomipramine *In Vitro* Reduces Glucocorticoid Receptor Function in Healthy Subjects but not in Patients with Major Depression. Neuropsychopharmacology 2008; 32:3182–3189; advance online publication, 26 March 2008; doi: 10:1038/npp.2008.44

These authors established that four of four glucocorticoids inhibited lipopolysaccharide-stimulated interleukin-6 levels equally in control subjects and in hypercortisolemic depressed patients. They then concluded that

> these findings do suggest glucocorticoid resistance in depressed patients: the fact that GR [glucocorticoid receptor] function was 'normal' in the face of such a big difference in plasma CORT [cortisol] in itself suggests a functional difference between patients and controls. Indeed, higher levels of CORT … would have been present in the *in vitro* milieu of depressed patients …

Actually, the 'big difference' is minimal. After a 10-fold dilution of the samples, mean cortisol concentrations *in vitro* are 1.56 ug/dl (42.9 nmol/l) in patients *vs* 0.88 ug/dl (24.2 nmol/l) in controls. Any difference in GR signal from these cortisol levels is negligible, considering the high concentrations of the tested glucocorticoids *in vitro* (see below). The data do not suggest any problem with glucocorticoid feedback signaling in hypercortisolemic depressed patients. This conclusion is consistent with a recent *in vivo* study (Carroll *et al*, 2007).

The IC_{50} for dexamethasone in the authors' whole blood test system is 60 nM (Rohleder *et al*, 2001, 2002), whereas the IC_{50} for dexamethasone inhibition of interleukin-6 production in isolated cell systems is 2–4 nM (Mulatero *et al*, 1997; Yehuda *et al*, 2004). It is 2–4 nM also against the GR *in vivo* (Dallman *et al*, 1989). Thus, the whole blood method used by Carvalho *et al*, 2008 is not a refined assay of GR sensitivity.

Unlike Rohleder *et al* (2001, 2002), who developed the method, the authors did not report adequate dose-response data and IC_{50} values. For dexamethasone, they reported only two concentrations, 10 and 100 nM. For comparison, the relevant concentrations in the clinical dexamethasone suppression test (DST) are 0.25–6 nM: above 6 nM the depression-DST signal is lost (Ritchie *et al*, 1990). Likewise, they reported only two cortisol concentrations, 1 and 10 uM (36 and 360 ug/dl), both far above the IC_{50} concentration. Complete dose-response and IC_{50} data are needed.

The authors stated that clomipramine (CMI) 10 uM antagonized the glucocorticoid effect in controls but not in patients. Clomipramine is clinically toxic at 10 uM, and it is cytotoxic at 40–100 uM (Yasuhara *et al*, 1985; Ying *et al*, 2002). In patients, trough plasma CMI concentrations are 0.05–1.0 uM (DUAG, 1999). Tricyclic antidepressant concentrations in cerebrospinal fluid are 7–10% of the total plasma levels (Kragh-Sorensen *et al*, 1976; Potter *et al*, 1979). The IC_{50} for CMI to inhibit norepinephrine and serotonin uptake by synaptosomes *in vitro* is 0.1 uM (Koe, 1973). Brain concentrations of tricyclic antidepressants may reach 5–7 uM (Glotzbach and Preskorn, 1982), but only 10% of that is free drug (Potter *et al*, 1979). Thus, 10 uM CMI as used by Carvalho *et al*, 2008 is excessive.

These limited data do not indicate impaired GR signaling in depression, and they do not 'clarify the interaction between antidepressants and glucocorticoids.' Those conclusions would require IC_{50} data in patients and control subjects, and evidence that CMI in clinically relevant concentrations altered the IC_{50} of dexamethasone or cortisol.

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