Drug News Perspect 19(10), December 2006

Available on the web at: www.prous.com/journals

LOOKING AHEAD

Antidepressant treatment has various effects on the hypothalamic–pituitary–adrenal axis, and there is support for the hypothesis that this axis has a larger role in the pathogenesis of major depression than previously thought.

The Effects of Antidepressants on the Hypothalamic–Pituitary–Adrenal Axis

by Brittany L. Mason and Carmine M. Pariante

Summary

Hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis has been found in some psychiatric disorders, especially in older patients with severe depression. Altered feedback inhibition, as demonstrated by increased circulating cortisol and nonsuppresssion of cortisol following administration of dexamethasone, may be to blame. Two glucocorticoid receptors control the HPA axis, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). MR regulates normal HPA fluctuations and the GR regulates in times of stress. Long-term antidepressant treatment in humans has been shown to upregulate both GR and MR in the brain, whereas short-term treatment has been shown to downregulate GR and MR. After 6–9 weeks of treatment GR function returns to normal, and the MR stays upregulated. Chronic antidepressant treatment in rodents has been shown to reduce HPA activity, even in the absence of GR or MR upregulation. These effects of antidepressants on HPA regulation may be attributed in part to regulation of the multidrug resistance protein transporter, P-glycoprotein. Finding relationships between antidepressant action and HPA regulation leads to the conclusion that the disruption of the HPA may be more a contributing factor to depression than other biological abnormalities.

The hypothalamic–pituitary–adrenal (HPA) axis is the body's stress response system and has also been found to be the main hormonal contributor in major depression. A hyperactive HPA axis can be found in patients with depression, and renormalization of the HPA axis precedes resolution of clinical symptoms. Antidepressant treatment has various effects on the HPA axis depending on the type of antidepressant and duration of treatment, and there is support for the hypothesis that the HPA axis has a larger role in the pathogenesis of major depression than first thought.

The HPA axis in major depression

The HPA axis is the main hormonal system involved in major depression, but the mechanisms underlying its abnormalities in patients with depression are still unclear. HPA axis activity is governed by the secretion of corticotropin releasing factor (CRF) and vasopressin (AVP) from the hypothalamus, which in turn activate the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary, which finally stimulates the secretion of glucocorticoids (cortisol in humans and corticosterone in rodents) from the adrenal cortex.[1,2] The glucocorticoids then interact with their receptors in multiple target tissues, including the HPA axis, where they are responsible for feedback inhibition of the secretion of ACTH from the pituitary and CRF from the hypothalamus. Although glucocorticoids regulate the function of

 CCC: 0214-0934/2006. DOI: 10.1358/dnp.2006.19.10.1068007

almost every tissue in the body, the best known physiological effect of these hormones is the regulation of energy metabolism (increased gluconeogenesis, increased lipolysis and increased protein degradation).

Hyperactivity of the HPA axis in major depression is one of the most consistent findings in psychiatry.[1–3] A significant percentage of depressed patients has been shown to hypersecrete cortisol, the endogenous adrenal glucocorticoid in humans, as manifested by increased 24-hour urinary free cortisol (UFC) and elevated plasma and cerebrospinal fluid (CSF) concentrations of cortisol. In addition, nonsuppression of cortisol, β-endorphin and ACTH following dexamethasone administration as well as blunted ACTH responses to CRF and an increased cortisol response to ACTH have been described. Increased volumes of the pituitary gland and of the adrenal glands are also present in depressed patients.

Interestingly, and consistent with the notion that HPA axis hyperactivity may be present across psychiatric disorders in the acute phase of the illnesses, we have recently demonstrated an increased volume of the pituitary gland in two independent samples of patients at their first episode of psychosis, including psychotic depression, psychotic mania and schizophrenia.[4,5] In general, HPA axis abnor- malities in major depression are most likely to occur in individuals who are older and more severely depressed.

The increased activity of the HPA axis is thought to be related, at least in part, to altered feedback inhibition by endogenous glucocorticoids. Endogenous glucocorticoids serve as potent negative regulators of HPA axis activity including the synthesis and release of CRF by neurons in the paraventricular nucleus.[6] Data supporting the notion that glucocorticoid-mediated feedback inhibition is impaired in major depression comes from a multitude of studies demonstrating nonsuppression of cortisol secretion following administration of the synthetic glucocorticoid dexamethasone (dexamethasone suppression test, DST), and more recent studies showing a lack of inhibition of ACTH responses to CRF following dexamethasone pretreatment (dexamethasone/CRF test).[1,7] While nonsuppression by dexamethasone in the DST and the dexamethasone/CRF test likely represent impaired feedback inhibition at the level of the pituitary,[6] impaired responsiveness to hydrocortisone challenge in depressed patients suggests these feedback alterations also occur in the brain,[8] although this latter finding has not been always replicated.[9] Furthermore, the existence of reduced HPA axis suppression by dexamethasone in first-degree relatives of depressed individuals suggests that altered feedback inhibition may represent a genetic (trait) vulnerability to the depressive disorders.[10,11] Finally, successful antidepressant treatment is associated with resolution of the impairment in the negative feedback on the HPA by glucocorticoids,[12,13] while persistence of nonsuppression after antidepressant treatment is associated with high risk of early relapse and a poor outcome after discharge.[14,15]

The glucocorticoid receptor

Glucocorticoids mediate their actions, including feedback regulation of the HPA axis, through two distinct intracellular corticosteroid receptor subtypes referred to as the type I, or mineralocorticoid, receptor (MR) and the type II, or glucocorticoid, receptor (GR).[6,16] The MR has a high affinity for endogenous corticosteroids and is believed to play a role in the regulation of circadian fluctuations in secretion of these hormones, especially the regulation of ACTH secretion during the diurnal trough in cortisol secretion. In contrast to the MR, the GR has a high affinity for dexamethasone and a lower affinity for endogenous corticosteroids. The GR is therefore believed to be more important when endogenous levels of glucocorticoids are high, such as in regulation of the stress response.[6,16] Because patients with major depression exhibit impaired HPA negative feedback in the context of elevated circulating levels of cortisol, a number of studies have considered the possibility that the number or function of GR, or both, are reduced in depressed patients. In fact, the DST specifically probes the GR only, as dexamethasone has a high affinity for the GR.[2] The only study that specifically examined MR-mediated negative feedback in depression, using an MR antagonist, found that this pathway is intact (or possibly oversensitive) in depressed patients.[17] Interestingly, we have developed a suppressive test using another synthetic glucocorticoid, prednisolone, which has a higher affinity for the MR and therefore should probe both receptors.[18] Using this test, we have indeed found that depressed patients have normal MR or hyperactive function as shown by a normal response to prednisolone together with an impaired response to dexamethasone.[19] However, most of the literature in this field has examined the GR. The GR is a ligand-induced transcription factor that belongs to the steroid/thyroid receptor superfamily.[2,6] Almost all cells of the body express the GR, but the number of receptors may vary between different cell types. Interestingly, data have demonstrated similar regulation of GR in the brain and in the immune system of laboratory animals. For example, Lowy[20] demonstrated that treatment of rats with reserpine, an amine-depleting drug that is known to induce depressive symptoms in humans and to produce dexamethasone nonsuppression in rats, decreases GR levels in the hippocampus, frontal cortex and pituitary as well as in lymphocytes and spleen. Similarly, Spencer et al.[21] found that both in the brain and in the immune system, GR is upregulated following adrenalectomy and downregulated following chronic treatment with corticosterone. Therefore, given limited access to brain GR in clinical populations, *in vitro* studies have been used to understand the molecular mechanisms underlying GR

abnormalities in patients with major depression.

The effects of antidepressants on corticosteroid receptors and the HPA axis in rodents

The most striking support to the hypothesis that abnormalities in the corticosteroid receptors contribute to the pathophysiology of major depression derives from animal and *in vitro* studies demonstrating a direct effect of antidepressants on the GR and the MR, leading to increased receptor expression and function and thus to increased negative feedback on the HPA axis. These studies support the clinical evidence that successful antidepressant treatment is associated with resolution of the glucocorticoid-mediated, negative-feedback impairment in the HPA axis[12,13,22] and also of glucocorticoid resistance in immune cells.[23]

A number of studies have shown that long-term antidepressant treatment upregulates GR and MR in the brain, including in the hippocampus and in the hypothalamus, and decreases basal and stress-induced glucocorticoid secretion. The vast majority of studies using tricyclic antidepressants (e.g., desipramine, amitriptyline, imipramine) or electroconvulsive shock has shown antidepressant-induced upregulation of brain GR, MR or both.[24–38] The tricyclic antidepressant clomipramine has also been found to decrease CRF mRNA levels in the paraventricular nucleus of Syrian hamsters.[39]

Studies examining selective serotonin reuptake inhibitor (SSRI) antidepressants (e.g., fluoxetine, citalopram, zimelidine) have found that chronic treatment with these antidepressants upregulates MR expression, while it has no effect on GR expression,[28,33,35,40–43] although one study found that a 2-day treatment with fluoxetine increases both MR and GR mRNAs in the hippocampus.[44] The antidepressant mirtazapine (which has a different mechanism of action compared with most other antidepressants, as it acts as an antagonist at presynaptic α_2-receptors and at postsynaptic 5-HT_2, 5-HT_3 and H_1 receptors with no inhibition of norepinephrine or serotonin reuptake) has also been shown to induce GR upregulation after 10 days of treatment in animals.[34]

Interestingly, the few studies that have looked at shorter treatment durations have found that antidepressants can acutely (within 3–9 days) induce a decrease of GR and MR expression. For example, Reul et al.[30] showed a decreased GR and MR expression after 3–7 days of amitriptyline and Yau et al.[45] showed that fluoxetine and venlafaxine (a serotonin and noradrenaline reuptake inhibitor) induce downregulation of GR and MR expression at 9 days. At the opposite end, studies looking at longer time points have indicated that GR expression returns to control levels after 6–9 weeks of treatment with antidepressants, while MR upregulation persists.[29,35,46] These animal data are consistent with the few clinical studies that have measured HPA axis changes following short-term antidepressant treatment. For example, we have recently demonstrated that 4 days of treatment with a therapeutic dose of citalopram increases glucocorticoid-mediated negative feedback of the HPA axis (measured as cortisol suppression by prednisolone) in healthy volunteers.[47]

Several of these studies have also shown that chronic treatment with antidepressants in rodents is associated with a reduction in basal and stress-induced HPA axis activity and that, surprisingly, GR or MR upregulation is not a prerequisite for this reduction.[2] Brady et al.[40] found that a 2-week treatment with fluoxetine, idazoxan or phenelzine reduced basal corticosterone levels in the absence of GR or MR upregulation. Montkowski et al.[48] demonstrated that long-term antidepressant treatment with moclobemide (a monoamine-oxidase inhibitor) induces normalization of the HPA axis in the absence of any changes in GR binding. Mukherjee et al.[49] also demonstrated that imipramine exerts glucocorticoid agonist-like effects with negative feedback on the HPA axis. However, phenelzine decreases glucocorticoid inhibition and stimulates the HPA axis as well as increasing adrenocortical sensitivity to ACTH.[50]

Interestingly, even shorter treatment with antidepressants is associated with an enhanced negative feedback on the HPA axis, possibly in the presence of a reduction, rather than an increase, in GR or MR expression. Yau et al.[45] found that a 9-day treatment with fluoxetine or venlafaxine induces a reduction in HPA axis activity together with the downregulation of GR and MR. Reul et al.[30] showed a decrease in adrenal weight, likely representing a decrease in HPA axis function, in rats treated with amitriptyline for 5 days, together with a decrease in hippocampal GR binding. This suggests that antidepressants can acutely decrease HPA axis activity by increasing the activation, rather than the expression, of the corticosteroid receptors—a model that is supported by several of our *in vitro* studies, and that seems to be related at least in part to the effects of antidepressants on membrane steroid transporters like the multidrug resistance P-glycoprotein.[51–55]

Finally, by using a stressor, the HPA can be disrupted to allow for independent analysis of how antidepressants affect a dysregulated system. For example, Delbende et al.[56] showed that a single injection of the antidepressant tianeptine, given 1–3 hours before a tube restraint stress, significantly reduced the stress-induced ACTH and corticosterone release in rats: an acute effect unlikely to be related to GR or MR upregulation. Prenatal stress decreases GR binding in the hippocampus of rats and administration of imipramine increases GR binding to levels similar to those of control animals,[57] thus illustrating how the antidepressant can induce an improperly working HPA to work as normal. Following restraint stress in rats, acute treatment with the SSRI citalopram lengthens the duration of

the heightened plasma corticosterone levels; however, chronic treatment with citalopram did not have an effect on the corticosterone levels but did prevent the ACTH response to the stressful situation.[49] Therefore, chronic treatment with an SSRI acts as a buffer to external stressors.

Conclusion

The final question is how these experimental effects are relevant to the effects of antidepressants in humans and in particular to the therapeutic effect of these drugs. In fact, the relationship between administration of antidepressants and regulation of the HPA axis is not clear. In humans, antidepressants have been shown to have different effects on the HPA axis, based on the duration of the treatment and the type of antidepressants. For example, Hesketh et al.[58] illustrated the different responses of the HPA axis following acute (activation of the HPA) and chronic (suppression of the HPA) administration of the SSRI. In addition, repeated treatment with citalopram in healthy controls was found to increase morning salivary cortisol secretion whereas the SSRI reboxetine did not,[59] thus indicating that there might be a dissociation between clinical effects and HPA axis effects. In contrast to other antidepressants, mirtazapine has been shown to inhibit salivary cortisol in patients with depression from the first administration of the drug[60] and to reduce cortisol and ACTH levels during the dexamethasone/CRF test one week following the initiation of treatment.[61]

In conclusion, the present data seem to support the hypothesis that the effects of antidepressants on the HPA axis may be mediated by more mechanisms than first thought. In many cases, the correction of HPA dysregulation precedes resolution of clinical symptoms. Finding relationships between antidepressant action and HPA regulation leads to the conclusion that the disruption of the HPA axis may be a more contributing factor to depression than other biological abnormalities. However, it is still unclear whether HPA dysregulation occurs in all cases of depression. It will therefore be beneficial to further investigate the specific antidepressant effects in correcting HPA abnormalities and to understand the molecular mechanisms underlying these specific effects.

Acknowledgment

Funded by the UK Medical Research Council and by the NARSAD.

References

1. Nemeroff, C.B. *The corticotropin-releasing factor (CRF) hypothesis of depression: New findings and new directions.* Mol Psychiatry 1996, 1: 336–42.
2. Pariante, C.M. and Miller, A.H. *Glucocorticoid receptors in major depression: Relevance to pathophysiology and treatment.* Biol Psychiatry 2001, 49: 391–404.
3. Pariante, C.M. *Glucorticoid receptor function in vitro in patients with major depression.* Stress 2004, 7: 209–19.
4. Pariante, C.M., Vassilopoulou, K., Velakoulis, D. et al. *Pituitary volume in psychosis.* Br J Psychiatry 2004, 185: 5–10.
5. Pariante, C., Brudaglio, F., Danese, A. et al. *Increased pituitary volume in patients of the AESOP first onset psychosis study.* Schizophr Res 2004, 67: 99–100.
6. de Kloet, E.R., Vreugdenhil, E., Oitzl, M.S. and Joels, M. *Brain corticosteroid receptor balance in health and disease.* Endocr Rev 1998, 19: 269–301.
7. Holsboer, F. *The corticosteroid receptor hypothesis of depression.* Neuropsychopharmacology 2000, 23: 477–501.
8. Young, E.A., Haskett, R.F., Murphy-Weinberg, V., Watson, S.J. and Akil, H. *Loss of glucocorticoid fast feedback in depression.* Arch Gen Psychiatry 1991, 48: 693–9.
9. Cooney, J.M. and Dinan, T.G. *Preservation of hypothalamic-pituitary-adrenal axis fast-feedback responses in depression.* Acta Psychiatr Scand 1996, 94: 449–53.
10. Lauer, C.J., Schreiber, W., Modell, S., Holsboer, F. and Krieg, J.C. *The Munich vulnerability study on affective disorders: Overview of the cross-sectional observations at index investigation.* J Psychiatr Res 1998, 32: 393–401.
11. Modell, S., Lauer, C.J., Schreiber, W., Huber, J., Krieg, J.C. and Holsboer, F. *Hormonal response pattern in the combined DEX-CRH test is stable over time in subjects at high familial risk for affective disorders.* Neuropsychopharmacology 1998, 18: 253–62.
12. Linkowski, P., Mendlewicz, J., Kerkhofs, M. et al. *24-Hour profiles of adrenocorticotropin, cortisol, and growth hormone in major depressive illness: Effect of antidepressant treatment.* J Clin Endocrinol Metab 1987, 65: 141–52.
13. Heuser, I.J., Schweiger, U., Gotthardt, U. et al. *Pituitary-adrenal-system regulation and psychopathology during amitriptyline treatment in elderly depressed patients and normal comparison subjects.* Am J Psychiatry 1996, 153: 93–9.
14. Zobel, A.W., Yassouridis, A., Frieboes, R.M. and Holsboer, F. *Prediction of medium-term outcome by cortisol response to the combined dexamethasone-CRH test in patients with remitted depression.* Am J Psychiatry 1999, 156: 949–51.
15. Zobel, A.W., Nickel, T., Sonntag, A., Uhr, M., Holsboer, F. and Ising, M. *Cortisol response in the combined dexamethasone/CRH test as predictor of relapse in patients with remitted depression: A prospective study.* J Psychiatr Res 2001, 35: 83–94.
16. McEwen, B.S., Biron, C.A., Brunson, K.W. et al. *The role of adrenocorticoids as modulators of immune function in health and disease: Neural, endocrine and immune interactions.* Brain Res Rev 1997, 23: 79–133.
17. Young, E.A., Lopez, J.F., Murphy-Weinberg, V., Watson, S.J. and Akil, H. *Mineralocorticoid receptor function in major depression.* Arch Gen Psychiatry 2003, 60: 24–8.
18. Pariante, C.M., Papadopoulos, A.S., Poon, L. et al. *A novel prednisolone suppression test for the hypothalamic-pituitary-adrenal axis.* Biol Psychiatry 2002, 51: 922–30.
19. Juruena, M., Cleare, A., Papadopoulos, A.S., Poon, L., Lightman, S. and Pariante, C.M. *Different response to dexamethasone and prednisolone in the same depressed patients.* Psychopharmacology (Berl) 2006, 189: 225–35.
20. Lowy, M.T. *Reserpine-induced decrease in type I and II corticosteroid receptors in neuronal and lymphoid tissues of adrenalectomized rats.* Neuroendocrinology 1990, 51: 190–6.
21. Spencer, R.L., Miller, A.H., Stein, M. and McEwen, B.S. *Corticosterone regulation of type I and type II adrenal steroid receptors in brain, pituitary, and immune tissue.* Brain Res 1991, 549: 236–46.
22. Ribeiro, S.C., Tandon, R., Grunhaus, L. and Greden, J.F. *The DST as a predictor of outcome in depression: A meta-analysis.* Am J Psychiatry 1993, 150: 1618–29.
23. Wodarz, N., Rupprecht, R., Kornhuber, J. et al. *Normal lymphocyte responsiveness to lectins but impaired sensitivity to in vitro glucocorticoids in major depression.* J Affect Disord 1991, 22: 241–8.
24. Kitayama, I., Janson, A.M., Cintra, A. et al. *Effects of chronic imipramine treatment on glucocorticoid receptor immunoreactivity in various regions of the rat brain. Evidence for selective increases of glucocorticoid receptor immunoreactivity in the locus coeruleus and in 5 hydroxytryptamine nerve cell groups of the rostral ventromedial medulla.* J Neural Transm 1998, 73: 191–203.
25. Young, E.A., Spencer, R.L. and McEwen, B.S. *Changes at multiple levels of the hypo-*

thalamo-pituitary adrenal axis following repeated electrically induced seizures. Psychoneuroendocrinology 1990, 15: 165–72.

26. Peiffer, A., Veilleux, S. and Barden, N. *Antidepressant and other centrally acting drugs regulate glucocorticoid receptor messenger RNA levels in rat brain.* Psychoneuroendocrinology 1991, 16: 505–15.
27. Brady, L.S., Whitfield, H.J. Jr., Fox, R.J., Gold, P.W. and Herkenham, M. *Long-term antidepressant administration alters corticotropin-releasing hormone, tyrosine hydroxylase, and mineralocorticoid receptor gene expression in rat brain: therapeutic implications.* J Clin Invest 1991, 87: 831–7.
28. Seckl, J.R. and Fink, G. *Antidepressants increase glucocorticoid and mineralocorticoid receptor mRNA expression in rat hippocampus in vivo.* Neuroendocrinology 1992, 55: 621–6.
29. Pepin, M.C., Pothier, F. and Barden, N. *Antidepressant drug action in a transgenic mouse model of the endocrine changes seen in depression.* Mol Pharmacol 1992, 42: 991–5.
30. Reul, J.M., Stec, I., Soder, M. and Holsboer, F. *Chronic treatment of rats with the antidepressant amitriptyline attenuates the activity of the hypothalamic-pituitary-adrenocortical system.* Endocrinology 1993, 133: 312–20.
31. Przegalinski, E., Budziszewska, B., Siwanowicz, J. and Jaworska, L. *The effect of repeated combined treatment with nifedipine and antidepressant drugs or electroconvulsive shock on the hippocampal corticosteroid receptors in rats.* Neuropharmacology 1993, 32: 1397–400.
32. Przegalinski, E. and Budziszewska, B. *The effect of long-term treatment with antidepressant drugs on the hippocampal mineralocorticoid and glucocorticoid receptors in rats.* Neurosci Lett 1993, 161: 215–8.
33. Budziszewska, B., Siwanowicz, J. and Przegalinski, E. *The effect of chronic treatment with antidepressant drugs on the corticosteroid receptor levels in the rat hippocampus.* Polish J Pharmacol 1994, 46: 147–52.
34. Peeters, B.W., van der, H.R., Gubbels, D.G. and Vanderheyden, P.M. *Effects of chronic antidepressant treatment on the hypothalamic-pituitary-adrenal axis of Wistar rats.* Ann NY Acad Sci 1994, 746: 449–52.
35. Rossby, S.P., Nalepa, I., Huang, M. et al. *Norepinephrine-independent regulation of GRII mRNA in vivo by a tricyclic antidepressant.* Brain Res 1995, 687: 79–82.
36. Yau, J.L., Olsson, T., Morris, R.G., Meaney, M.J. and Seckl, J.R. *Glucocorticoids, hippocampal corticosteroid receptor gene expression and antidepressant treatment: Relationship with spatial learning in young and aged rats.* Neuroscience 1995, 66: 571–81.
37. Eiring, A. and Sulser, F. *Increased synaptic availability of norepinephrine following desipramine is not essential for increases in GR mRNA. Short communication.* J Neural Transm 1997, 104: 1255–8.
38. Johansson, I.M., Bjartmar, L., Marcusson, J., Ross, S.B., Seckl, J.R. and Olsson, T. *Chronic amitriptyline treatment induces hippocampal NGFI-A, glucocorticoid receptor and mineralocorticoid receptor mRNA expression in rats.* Mol Brain Res 1998, 62: 92–5.
39. Cordner, A.P., Herwood, M.B., Helmreich, D.L. and Parfitt, D.B. *Antidepressants blunt the effects of inescapable stress on male mating behaviour and decrease corticotrophin-releasing hormone mRNA expression in the hypothalamic paraventricular nucleus of the Syrian hamster (Mesocricetus auratus).* J Neuroendocrinol 2004, 16: 628–36.
40. Brady, L.S., Gold, P.W., Herkenham, M., Lynn, A.B. and Whitfield, H.J. Jr. *The antidepressants fluoxetine, idazoxan and phenelzine alter corticotropin-releasing hormone and tyrosine hydroxylase mRNA levels in rat brain: Therapeutic implications.* Brain Res 1992, 572: 117–25.
41. Lopez, J.F., Chalmers, D.T., Little, K.Y. and Watson, S.J. *Regulation of serotonin1A, glucocorticoid, and mineralocorticoid receptor in rat and human hippocampus: Implications for the neurobiology of depression.* Biol Psychiatry 1998, 43: 547–73.
42. Bjartmar, L., Johansson, I.M., Marcusson, J., Ross, S.B., Seckl, J.R. and Olsson, T. *Selective effects on NGFI-A, MR, GR and NGFI-B hippocampal mRNA expression after chronic treatment with different subclasses of antidepressants in the rat.* Psychopharmacology (Berl) 2000, 151: 7–12.
43. Yau, J.L., Hibberd, C., Noble, J. and Seckl, J.R. *The effect of chronic fluoxetine treatment on brain corticosteroid receptor mRNA expression and spatial memory in young and aged rats.* Mol Brain Res 2002, 106: 117–23.
44. Semont, A., Fache, M., Hery, F., Faudon, M., Youssouf, F. and Hery, M. *Regulation of central corticosteroid receptors following short-term activation of serotonin transmission by 5-hydroxy-l tryptophan or fluoxetine.* J Neuroendocrinol 2000, 12: 736–44.
45. Yau, J.L., Noble, J., Hibberd, C. and Seckl, J.R. *Short-term administration of fluoxetine and venlafaxine decreases corticosteroid receptor mRNA expression in the rat hippocampus.* Neurosci Lett 2001, 306: 161–4.
46. Reul, J.M., Labeur, M.S., Grigoriadis, D.E., De Souza, E.B. and Holsboer, F. *Hypothalamic-pituitary adrenocortical axis changes in the rat after long-term treatment with the reversible monoamine oxidase-A inhibitor moclobemide.* Neuroendocrinology 1994, 60: 509–19.
47. Pariante, C.M., Papadopoulos, A.S., Poon, L. et al. *Four days of citalopram increase suppression of cortisol secretion by prednisolone in healthy volunteers.* Psychopharmacology (Berl) 2004, 177(1–2): 200–6.
48. Montkowski, A., Barden, N., Wotjak, C. et al. *Long-term antidepressant treatment reduces behavioural deficits in transgenic mice with impaired glucocorticoid receptor function.* J Neuroendocrinol 1995, 7: 841–5.
49. Mukherjee, K., Knisely, A. and Jacobson, L. *Partial glucocorticoid agonist-like effects of imipramine on hypothalamic-pituitary-adrenocortical activity, thymus weight, and hippocampal glucocorticoid receptors in male C57BL/6 mice.* Endocrinology 2004, 145: 4185–91.
50. Kier, A., Han, J. and Jacobson, L. *Chronic treatment with the monoamine oxidase inhibitor phenelzine increases hypothalamic-pituitary-adrenocortical activity in male C57BL/6 mice: Relevance to atypical depression.* Endocrinology 2005, 146: 1338–47.
51. Pariante, C.M., Pearce, B.D., Pisell, T.L., Owens, M.J. and Miller, A.H. *Steroid-independent translocation of the glucocorticoid receptor by the antidepressant desipramine.* Mol Pharmacol 1997, 52: 571–81.
52. Pariante, C.M., Makoff, A., Lovestone, S. et al. *Antidepressants enhance glucocorticoid receptor function in vitro by modulating the membrane steroid transporters.* Br J Pharmacol 1997, 134:1335–43.
53. Pariante, C.M., Kim, R.B., Makoff, A. and Kerwin, R.W. *Antidepressant fluoxetine enhances glucocorticoid receptor function in vitro by modulating membrane steroid transporters.* Br J Pharmacol 2001, 139: 1111–8.
54. Pariante, C.M., Hye, A., Williamson, R., Makoff, A., Lovestone, S. and Kerwin, R.W. *The antidepressant clomipramine regulates cortisol intracellular concentrations and glucocorticoid receptor expression in fibroblasts and primary rat neurones.* Neuropsychopharmacology 2003, 28: 1553–61.
55. Pariante, C.M., Thomas, S.A., Lovestone, S., Makoff, A. and Kerwin, R.W. *Do antidepressants regulate how cortisol affects the brain?* Psychoneuroendocrinology 2004, 29: 423–47.
56. Delbende, C., Contesse, V., Mocaer, E., Kamoun, A. and Vaudry, H. *The novel antidepressant, tianeptine, reduces stress-evoked stimulation of the hypothalamo-pituitary-adrenal axis.* Eur J Pharmacol 1991, 202: 391–6.
57. Morley-Fletcher, S., Darnuadery, M., Mocaer, E. et al. *Chronic treatment with imipramine reverses immobility behaviour, hippocampal corticosteroid receptors and*

cortical 5-HT(1A) receptor mRNA in prenatally stressed rats. Neuropharmacology 2004, 47: 841–7.

58. Hesketh, S., Jessop, D.S., Hogg, S. and Harbuz, M.S. *Differential actions of acute and chronic citalopram on the rodent hypothalamic-pituitary-adrenal axis response to acute restraint stress.* J Endocrinol 2005, 185: 373–82.
59. Harmer, C.J., Bhagwagar, Z., Shelley, N. and Cowen, P.J. *Contrasting effects of citalopram and reboxetine on waking salivary cortisol.* Psychopharmacology (Berl) 2003, 167: 112–4.
60. Laakmann, G., Hennig, J., Baghai, T. and Schule, C. *Mirtazapine acutely inhibits salivary cortisol concentrations in depressed patients.* Ann NY Acad Sci 2004, 1032: 279–82.
61. Schule, C., Baghai, T., Rackwitz, C. and Laakmann, G. *Influence of mirtazapine on urinary free cortisol excretion in depressed patients.* Psychiatry Res 2003, 15: 257–64.

Brittany L. Mason is a PhD student and Carmine M. Pariante is Senior Lecturer and MRC Clinician Scientist Fellow in the Stress, Psychiatry, and Immunology Lab, Institute of Psychiatry King's College London, London, United Kingdom. *Correspondence: Carmine M. Pariante, 1 Windsor Walk, Denmark Hill, London SE5 8AF, UK. Tel: +44-20-78480807; Fax: +44-20-78480051; E-mail: c.pariante@iop.kcl.ac.uk.*