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GUEST EDITORIAL

Melancholic and atypical subtypes of depression represent distinct pathophysiological entities: CRH, neural circuits, and the diathesis for anxiety and depression

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Two outstanding papers appear in this month's issue, with significant clinical implications related to the role of stress mediators in the pathophysiology of affective illness. The first of these studies, by Lamers *et al.*,[1] in over 200 patients and 500 controls, confirms our earlier suggestion that studies of depressive disorder should be stratified to examine melancholic and atypical depression separately. They report that the hypothalamic–pituitary–adrenal (HPA) axis, and several inflammatory and metabolic mediators differ between patients with melancholic and atypical depression. While the HPA axis findings are unequivocal, the findings regarding inflammatory and metabolic parameters, although interesting, will need replication in patients and controls closely matched for body mass index (BMI). This paper represents an archival contribution to the literature.

The second study by Rogers *et al.*[2] elucidates the relations between the propensity for anxiety and depression, the corticotropin-releasing hormone receptor 1 (CRHR1) genotype and the metabolic activity of key brain neurocircuits in 246 rhesus macaques. This study was elegantly designed and executed and is also of archival quality.

Lamers *et al.* studied 111 patients with chronic melancholic depression, 122 with chronic atypical depression and 543 controls. The authors state that the chronic forms of these illnesses have higher heritability.[3] Melancholic patients were identified as those depressed patients who had diminished appetite and body weight loss, whereas atypical patients were those who had increased appetite and weight gain. Of these, approximately 30% were severely depressed, 40% of moderate severity and 40% of lower severity. There were more women than men, whereas patients with melancholic depression had a higher rate of smoking.

Melancholics had significantly higher levels of cortisol than those with atypical depression or controls. On the other hand, plasma cortisol levels were similar in atypical patients and controls. In addition, patients with atypical depression had increased measures of abdominal circumference and BMI, and higher circulating levels of C-reactive protein, interleukin (IL)-6 and tumor necrosis factor (TNF)-α. They also had higher levels of plasma triglycerides and glucose and lower levels of high-density lipoprotein cholesterol than patients with melancholic depression.

It should be noted that visceral fat constitutes a very large reservoir of inflammatory cytokines, including IL-6 and TNF-α,[4] and secretes these into the hepatic portal circulation, influencing liver function. Plasma IL-6 and TNF-α levels correlate with BMI,[5] and it is estimated that approximately 40% of the circulating levels of IL-6 are derived from visceral fat. With correction of BMI, levels of C-reactive protein and IL-6 were no longer significantly elevated, but the levels of TNF-α remained significantly higher than in melancholics. BMI corrections were not included for the levels of triglycerides, glucose and high-density lipoprotein cholesterol. Measures of glucose metabolism and lipids are extremely sensitive to body weight and BMI. It is thus quite possible that these may be artifacts of BMI rather than intrinsic to the disorder of atypical depression. It might be informative to construct a surrogate analysis with melancholics and atypicals very closely matched for BMI.

The authors state that atypical patients resemble those with metabolic syndrome, and this is clearly true with respect to abdominal circumference, BMI and TNF-α levels. However, the patients with atypical depression had lower rather than higher blood pressure levels than controls. The authors could not account for this finding.

We have been interested in possible differences between melancholic and atypical patients for over 20 years.[6] One of our primary interests has been to determine the extent to which patients who are depressed with atypical profiles actually have a hypoactive HPA axis compared with controls. This goal was stimulated in part by the fact that in addition to body weight and BMI, melancholic and atypical depressions are the antithesis of one another in other dimensions. Patients with melancholic depression have insomnia and early morning awakening, whereas subjects with atypical depression are hypersomnic. The diurnal patterns in mood are also strikingly different between these subgroups. Patients with melancholia feel worse in the morning with slight amelioration as the day progresses, while those with atypical depression feel best in the morning, with deterioration as the day progresses. Although not as consistent, patients with melancholic depression tend to be hyperaroused, whereas those with atypical depression are often hypoaroused and extremely fatigued. Taken together, the increased sleep, food intake and fatigue in atypical depression suggested a decrement in stress system activity, including the HPA axis and the sympathetic system.

The decrease in HPA axis activity in atypical depression could be difficult to demonstrate through measurements of basal circulating cortisol levels, and might require other strategies for its documentation. We found that medication-free patents with seasonal affective disorder who met all of the criteria for atypical depression demonstrated responses to CRH virtually identical to those seen in patients with other known forms of hypothalamic CRH deficiency whom we had studied.[7,8] Patients with seasonal affective disorder had delayed, diminished adrenocortical trophic hormone (ACTH) and cortisol responses to exogenous CRH and decreased adrenal cortisol responses to the ACTH released during CRH stimulation, revealing that the adrenal cortex had been chronically insufficiently stimulated by the hypothalamic–pituitary components of the HPA axis. Using the identical CRH stimulation test, ACTH and cortisol assays, we were able to show that patients with predominantly melancholic depression had clear evidence of baseline hypercortisolism, blunted ACTH responses and exaggerated cortisol responses to the ACTH released during CRH stimulation,[9,10] compatible with excessive hypothalamic–pituitary activation of the adrenal cortex. We also demonstrated that patients with Cushing disease, whose depressions are atypical,[11] have cerebrospinal fluid (CSF) CRH levels that are strikingly reduced compared with controls. These findings need to be replicated in a larger series of patients with classic atypical depression.

Reduced activity of the HPA axis in atypical depression would help explain increased secretion of immune mediators in this disorder. Decreased cortisol secretion is systematically associated with disinhibition of the immune system, as cortisol exerts tonic inhibitory effects on immune function even.[12,13]

One other point about cortisol secretion in patients with melancholic depression deserves mention. We studied the levels of plasma cortisol and norepinephrine (NE), CSF NE and CSF CRH in samples taken hourly for 24 h in medication-free severely depressed melancholic patients. We found that plasma cortisol, plasma NE and CSF NE were all significantly elevated compared with controls.[14,15] In addition, plasma cortisol, plasma NE and CSF NE were secreted in phase. Their diurnal variations were virtually identical and their moment-to-moment secretion was significantly correlated.[14,15] These data indicate that hypercortisolemic patients with melancholic depression have increased levels of plasma NE as well. Given the confluence of plasma cortisol and NE secretion, it is conceivable that patents with atypical depression have decreased sympathetic nervous system activity that could be a factor in their significant reductions in blood pressure observed in the study of Lamers *et al*.[1]

An examination of the 24-h curves in the above studies showed that the arousal-producing compounds cortisol and NE are peaking in the morning, corresponding to the period of the maximal severity of depressive symptoms in patients with melancholia, who are often hyperaroused. Conversely, the hypoaroused atypical patients respond well to the peak levels of these arousing producing hormones in the morning, and accordingly, feel best in the AM.

Rogers *et al*.[2] in Ned Kalin's group examined rhesus macaques for features of anxious temperament, the degree to which anxious temperament was associated with specific single-nucleotide polymorphisms (SNPs) in the *CRHR1* gene, and whether these SNPs correlated with measures of metabolism in key brain regions involved in anxiety and depressive disorders.

There have been several prior studies examining the relations between the *CRHR1* gene and either depressive or anxiety disorders. Liu *et al*.[16] reported an association of a *CRHR1* gene SNP and haplotype with major depression. Polanczyk *et al*.[17] found a protective effect of a CRHR1 variant on the development of adult depression following childhood maltreatment. Licinio *et al*.[18] showed a relation of a polymorphism in the *CRHR1* gene and response to antidepressants. However, no one had shown relations between specific SNPs in coding and non-coding regions of the *CRHR1* gene and a behavioral phenotype, as well as a significant interaction between these SNPs and metabolic activity in areas of the brain.

In young rhesus monkeys, anxious temperament is analogous to the childhood risk phenotype that predicts development of human anxiety and depressive disorders. Rogers *et al*.[2] studied 236 young rhesus monkeys raised in normally nurturing environments with their mothers who were subsequently tested for evidence of an anxious temperament. In all 236 macaques, they examined the sequence variation of the *CRHR1* gene and assessed regional brain metabolism by ^{18}F-labelled fluoro-2-deoxyglucose positron emission tomography.

The authors found two SNPs in exon 6 that were independently associated with anxious temperament. Specifically, they identified SNP 4805, a splice site mutation, and another variant, SNP 5043, which alters the amino-acid sequence of the CRHR1. They also found yet another SNP associated with anxious temperament in the 5′ region, suggesting a possible alteration in the promoter sequence that regulates expression of the *CRHR1* gene. The authors then noted association of these SNPs to alterations in metabolic activity in the hippocampus and the amygdala, two areas clearly involved in the pathophysiology of mood disorders, as well as the intraparietal sulcus and precuneus. It should be noted that exon 6 is present only in the CRHR1 splice variant CRHR1b. These data indicate that these SNPs influence both behavioral phenotype and metabolism in brain sites crucial to affective illness and anxiety, and represent the first data to implicate the CRHR1b splice variant in the pathogenesis of anxiety and depression.

These findings are not surprising in the light of the multiplicity of roles that CRH has and that implicate it in the pathogenesis of affective disorders (reviewed in refs 19–21). The intraventricular infusion of CRH in rodents sets into motion features that resemble behavioral features of depressive disorders that include anxiety, hyperarousal and fear-related behaviors.[21] CRH also sets into motion many of the physiologic components of melancholic depression as well, including activation of the HPA axis and sympathetic nervous system,[22] and inhibition of the growth hormone, gonadal and thyroid axes. Finally, CRH elicits the neurovegetative components of melancholia, including loss of appetite, insomnia and decreased sexual behavior.[21,23,24] CRH thought to be released from postganglionic sympathetic terminals is also a potent stimulus to the innate immune system,[25] whereas a CRH antagonist significantly lowers the activation of inflammatory response to immunogenic stimuli.[26] We found that our specific CRHR1 antagonist antalarmin given to rhesus macaques significantly diminished the social stressor-induced responses of plasma ACTH, cortisol, and NE, and CSF CRH.[27]

Documenting increased CRH secretion in depression has required, in addition to assessment of basal cortisol and ACTH levels, the indirect estimation of CRH levels. We first reported data indicating CRH hypersecretion in depression utilizing the CRH stimulation test[10] a finding replicated several months later by Holsboer's group.[28] Subsequently, Holsboer's group developed the dexamethasone/CRH test,[29] which has become the predominant test used to assess HPA function in psychiatric patients, and has yielded important correlations between HPA axis function and other parameters.[30]

In contrast to the study by Nemeroff *et al*.[31] reporting increased CSF CRH, six other studies have not replicated this result,[15,32–36] including one in which Nemeroff is a co-author.[34] This does not mean that normal levels of CSF CRH denote normative CRH secretion in the hyperactive HPA axis function of melancholics. In our study measuring plasma cortisol and NE, and CSF NE and CRH in medication free, severely melancholic depressed patients hourly for 24 h, we found that the levels of plasma ACTH and CSF CRH, which are both highly glucocorticoid suppressible, were similar in patients and controls in the face of pronounced hypercortisolism and hypersecretion of NE into plasma and CSF.[15] In this setting, the adrenals had become hyperresponsive to ACTH in the context of sustained hypothalamic–pituitary activation of the adrenal cortex. If the central set-point for cortisol secretion had normalized, plasma ACTH levels should have fallen below normal to produce normal levels of plasma cortisol. Their remaining 'normal' in this setting, permitted the increased central set point for cortisol secretion to produce the requisite hypercortisolism via 'normal' plasma ACTH levels. The same can be said for CSF CRH. Thus, their 'normal' levels were inappropriate for the state of adrenal hyperresponsiveness and for the degree of baseline hypercortisolism seen in these patients. Soon after electroconvulsive treatment-induced remission of these patients, with the hyperresponsiveness of the adrenals not yet resolved, plasma ACTH and CSF CRH were substantially lower than in controls, with a trend for reduced CSF CRH levels in the recovered patients (unpublished observations). In addition to the other negative studies, the only other study of repeated measures of CSF CRH taken over time in depressed patients, by Geracioti *et al*.,[33] also failed to document increased CSF CRH levels.

The findings of Rogers *et al*.[2] implicating an association with SNPs in the CRHR1b splice variant, neural circuits, and the diathesis for anxiety and depression could mean that there is hyperactivity of the CRH system without there necessarily being

hypersecretion of CRH *per se* in depressive and anxiety disorders. However, the weight of indirect evidence of functional CRH hypersecretion in depression suggests that both mechanisms might be working simultaneously. Given the preferential activation of the HPA axis in melancholic patients, we have previously suggested on a number of occasions that studies using CRH antagonists in the treatment of depression should be preferentially administered to melancholic patients. It is our suggestion that including atypicals in CRH antagonist studies in depression may defeat the purpose of these studies, as no improvement or even deterioration of symptomatology, may occur.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1 Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman AT, Penninx BW. *Mol Psychiatry* 2013 (in press).
2 Rogers J, Raveendran M, Fawcett GL, Fox AS, Shelton SE, Oler JA *et al. Mol Psychiatry* 2013 (in press).
3 Levinson DF, Zubenko GS, Crowe RR, DePaulo RJ, Scheftner WS, Weissman MM *et al. Am J Med Genet B Neuropsychiatr Genet* 2003; **119B**: 118–130.
4 You T, Yang R, Lyles MF, Gong D, Nicklas BJ. *Am J Physiol Endocrinol Metab* 2005; **288**: E741–E747.
5 Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K, Chrousos GP. *J Clin Endocrinol Metab* 1997; **82**: 1313–1316.
6 Gold PW, Chrousos GP. *Mol Psychiatry* 2002; **7**: 254–275.
7 Joseph-Vanderpool JR, Rosenthal NE, Chrousos GP, Wehr TA, Skwerer R, Kasper S *et al. J Clin Endocrinol Metab* 1991; **72**: 1382–1387.
8 Avgerinos PC, Chrousos GP, Nieman LK, Oldfield EH, Loriaux DL, Cutler Jr. GB. *J Clin Endocrinol Metab* 1987; **65**: 906–913.
9 Gold PW, Loriaux DL, Roy A, Kling MA, Calabrese JR, Kellner CH *et al. N Engl J Med* 1986; **314**: 1329–1335.
10 Gold PW, Chrousos G, Kellner C, Post R, Roy A, Augerinos P *et al. Am J Psychiatry* 1984; **141**: 619–627.
11 Dorn LD, Burgess ES, Dubbert B, Simpson SE, Friedman T, Kling M *et al. Clin Endocrinol* 1995; **43**: 433–442.
12 Sternberg EM, Young 3rd WS, Bernardini R, Calogero AE, Chrousos GP, Gold PW *et al. Proc Natl Acad Sci USA* 1989; **86**: 4771–4775.
13 Sternberg EM, Hill JM, Chrousos GP, Kamilaris T, Listwak SJ, Gold PW *et al. Proc Natl Acad Sci USA* 1989; **86**: 2374–2378.
14 Gold PW, Wong ML, Goldstein DS, Gold HK, Ronsaville DS, Esler M *et al. Proc Natl Acad Sci USA* 2005; **102**: 8303–8308.
15 Wong ML, Kling MA, Munson PJ, Listwak S, Licinio J, Prolo P *et al. Proc Natl Acad Sci USA* 2000; **97**: 325–330.
16 Liu Z, Zhu F, Wang G, Xiao Z, Wang H, Tang J *et al. Neurosci Lett* 2006; **404**: 358–362.
17 Polanczyk G, Caspi A, Williams B, Price TS, Danese A, Sugden K *et al. Arch Gen Psychiatry* 2009; **66**: 978–985.
18 Licinio J, O'Kirwan F, Irizarry K, Merriman B, Thakur S, Jepson R *et al. Mol Psychiatry* 2004; **9**: 1075–1082.
19 Gold PW, Goodwin FK, Chrousos GP. *N Engl J Med* 1988; **319**: 348–353.
20 Gold PW, Goodwin FK, Chrousos GP. *N Engl J Med* 1988; **319**: 413–420.
21 Sutton RE, Koob GF, Le Moal M, Rivier J, Vale W. *Nature.* 1982; **297**: 331–333.
22 Brown MR, Fisher LA, Spiess J, Rivier C, Rivier J, Vale W. *Endocrinology.* 1982; **111**: 928–931.
23 Sirinathsinghji DJ, Rees LH, Rivier J, Vale W. *Nature.* 1983; **305**: 232–235.
24 Britton DR, Koob GF, Rivier J, Vale W. *Life Sci* 1982; **31**: 363–367.
25 Karalis K, Sano H, Redwine J, Listwak S, Wilder RL, Chrousos GP. *Science* 1991; **254**: 421–423.
26 Webster EL, Barrientos RM, Contoreggi C, Isaac MG, Ligier S, Gabry KE *et al. J Rheumatol* 2002; **29**: 1252–1261.
27 Habib KE, Weld KP, Rice KC, Pushkas J, Champoux M, Listwak S *et al. Proc Natl Acad Sci USA.* 2000; **97**: 6079–6084.
28 Holsboer F, Von Bardeleben U, Gerken A, Stalla GK, Muller OA. *N Engl J Med* 1984; **311**: 1127.
29 Heuser I, Yassouridis A, Holsboer F. *J Psychiatric Res.* 1994; **28**: 341–356.
30 Menke A, Samann P, Kloiber S, Czamara D, Lucae S, Hennings J *et al. Psychoneuroendocrinology.* 2012; **37**: 565–575.
31 Nemeroff CB, Widerlov E, Bissette G, Walleus H, Karlsson I, Eklund K *et al. Science* 1984; **226**: 1342–1344.
32 Garakani AMJ, Yehuda R, Gorman JM. *J Affective Dis* 2012.
33 Geracioti Jr TD, Orth DN, Ekhator NN, Blumenkopf B, Loosen PT. *J Clin Endocrinol Metab* 1992; **74**: 1325–1330.
34 Heuser I, Bissette G, Dettling M, Schweiger U, Gotthardt U, Schmider J *et al. Depress Anxiety* 1998; **8**: 71–79.
35 Kling MA, Roy A, Doran AR, Calabrese JR, Rubinow DR, Whitfield Jr HJ *et al. J Clin Endocrinol Metab* 1991; **72**: 260–271.
36 Roy A, Pickar D, Paul S, Doran A, Chrousos GP, Gold PW. *Am J Psychiatry* 1987; **144**: 641–645.