Relation of genes regulating the HPA-axis to major depression and suicidality; novel findings¹⁾

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Major depression (MD) is one of the most costly diseases in the world (Wasserman, 2006). Untreated affective disorders tend to be chronic and also life-threatening, since depression commonly precedes suicide. In the clinic, these patients must be assessed for their risk of suicide, as it is estimated to be the cause of death in 10-15% of individuals with MD (Wasserman, 2006). To expand the possibilities of intervention and therapy of suicidality, particularly in connection to the treatment of MD, its neurobiological causality is being explored (Mann, 2003; Wasserman, 2001).

In a stress-vulnerability model, genetic set-up, as well as environmental exposure to psychological stress, contributes to a person's predisposition for suicidality, as well as to MD (Hasler et al., 2004; Mann, 2003; Wasserman, 2001). The main neurochemical findings on suicidality have suggested alterations in neurosystems which are usually implicated in MD; a lowered serotonergic (5HT) activity, depletion of the noradrenergic (NA) system and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Whereas the genes of e.g. the 5HT system and of the key NA-biosynthesis enzyme, tyrosine hydroxylase, have been studied extensively in this context (Bondy et al., 2006; Rujescu et al., 2007), the genes in the HPA axis have only begun to be investigated recently.

An over-active HPA axis is also the most consistent neurobiological indicator of MD (Bale, 2005; Hasler et al., 2004; Nemeroff & Vale, 2005; Roy et al., 1987; Swaab et al., 2005). This is true also true for some suicidal individuals, as an over-active HPA axis, particularly in connection to depression, is often preceding suicide (Coryell & Schlesser, 2001; Young, 2005). The HPA-activity is primarily attributed to the action of corticotropin releasing hormone (CRH) and by altered feedback regulation of the axis through the glucocorticoid and mineralocorticoid receptors, which is manifested as hypercortisolemia and a failure to suppress cortisol. CRH alterations have also been observed in extrahypothalamic brain regions, e.g. the frontal cortex, limbic regions and cerebro spinal fluid (CSF). CRH acts as the key mediator of

behavioral, cognitive, autonomic, neuro-endocrine and immunologic responses to aversive stimuli (emotional and physical stress or inflammation), acting mainly through the CRH receptor 1 (CRHR1). In the HPA axis, CRH binds to CRHR1s in the anterior pituitary. This results in production of proopiomelanocortin (POMC)-derived peptides, such as adrenocorticotrophic hormone (ACTH), which in turn stimulate the adrenal gland to secrete glucocorticoids (but also mineralocorticoids and androgens). The steroid act on GRs and MRs in many tissues, including the brain, particularly parts of the brain stem and limbic regions. A functional response in the feedback regulation, occurring through the balanced activation of GRs and MRs, as well as by downregulating the expression of CRHR1 in the pituitary (Aguilera et al., 2004), is crucial for returning to a normal state. A chronic state of CRH-mediated activity, e.g. due to adverse environmental stress or defective coping with low levels of stress, may result in disruption of the HPA axis feedback with consequences for e.g. the innervating limbic functions. Monoaminergic neurotransmission is affected, by e.g. suppression of the 5-HT receptor 1a in the dorsal raphe nuclei (Meijer & de Kloet, 1998) or by affecting NA in locus coeruleus (LC). Parallel effects of high levels of CRH (by action through its receptors), includes the increased release of pro-inflammatory cytokines by immune cells, activating the indoleamine 2,3-dioxygenase (IDO) pathway, with subsequent consequences of tryptophan-(5HT)-depletion and neurotoxicity, as well as glutamatergic hyperfunction (Leonard, 2005; Muller & Schwarz, 2007). Thus, disturbances in HPA axis responsiveness connected to CRH, are relevant in MD, as well as in suicidality.

The effects of CRH dysregulation are primarily mediated through CRHR1. Consequently, antagonists active against CRHR1 are being developed as a novel type of antidepressants (Nielsen, 2006). From a pharmacogenomic perspective, it is of importance to have access to the level of individual variation in this gene in context to its functionality, which can be needed for evaluation of treatment efficacy as well as being used in diagnostic tools.

Knowledge about dysfunctional CRHR1 variants may also bring about new, highly specific treatment possibilities with inhibitory RNAs (Sah, 2006). Surprisingly little is known about influence of genetic variations in the CRHR1 gene in the context of stress and depression, since only a few such studies have been reported up to date (Licinio et al., 2004; Liu et al., 2007; Liu et al., 2006; Papiol et al., 2007; Wasserman et al., 2007). In fact, our group has been the first to study the genetic variation in the CRHR1 gene in connection to depression and stress among suicidal individuals (Wasserman et al., 2007).

Genetic variation in CRHR1 showed association and linkage to suicide attempt in depressed males exposed to low levels of stress. This association to low stress was true also for female suicide attempters, but without relation to depression. This may reflect the genetics behind the fact that a higher proportion of the depressed males have been shown to be suicidal, compared with depressed females (Wasserman, 2001). Although there is need of further confirmation of our novel finding and analysis of the CRHR1 locus, we hypothesized that these individuals may be genetically predisposed to react with dysregulated HPA activity upon a low threshold of stress, through some alterations of the CRHR1 gene expression or functionality, possibly experiencing a chronic state of HPA activation and/or a reduced feed-back mechanism, which partly substitute the environmental influence of high levels of stressful life events in the suicidal process (Wasserman et al., 2007). Interestingly our previous novel findings demonstrated that genetic

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variation in a transcription factor of the POMC gene, TBX19, which is regulated by CRH, showed association and linkage to the anger / hostility personality trait and suicidality (Wasserman et al., 2006). Taken together, our result suggest that genetic variation in the CRH-mediated regulation of the HPA axis is a factor of importance in suicidality and, as other have shown as well, for MD.

A thorough understanding of the dysregulation occurring at the HPA axis in suicidality is however only in its infancy. Whereas the dexamethasone suppression test (DST) is proving itself as an increasingly more viable prognostic test for the suicidality among certain depressed individuals, there is a substantial need for inclusion of additional measurement variables (Coryell & Schlesser, 2007; Coryell et al., 2006; Mann et al., 2006). For example, there is a need to explain the observed reduction in HPA axis activity in connection to suicidality (Pfennig et al., 2005), as well as to be able to differentiate from non-suicidal patients with MD. Since feedback in the HPA axis occurs both at the level of glucocorticoid receptors, as well as CRHR1 in the pituitary, it is likely that genetic variation in several genes of this system must taken into account in evaluating such results. Moreover, other suicidal individuals show lowered 5HT activity and yet others may show variation in further neurobiological systems (Mann, 2003; Wasserman, 2001). This is of interest in light of that the HPA axis is complexly interconnected with many of these neurosystems, e.g. monoaminergic and glutamatergic (Leonard, 2005; Meijer & de Kloet, 1998; Muller & Schwarz, 2007), and that the understanding of this network is likely to require a more detailed dissection of the variabilities in these genes, as well as a consideration of interacting or redundant effects between genes, in the context of environmental stress (Kendler, 2005).

Thus, the exploration of the HPA axis at the level of genetic variability hold promises of delivering significant explanations as to why certain individuals are at risk for suicidality, in connection to MD or other conditions of stress, as well as being seemingly necessary for the construction of reliable diagnostic and treatment tools, with sufficient sensitivity and specificity for the suicidal aspect of these patients.

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References

- Aguilera, G., Nikodemova, M., Wynn, P. C., & Catt, K. J. (2004). **Corticotropin releasing hormone receptors: Two decades later.** *Peptides*, 25(3), 319-329.
- Bale, T. L. (2005). **Sensitivity to stress: Dysregulation of CRF pathways and disease development.** *Hormones and Behaviour*, 48, 1-10.
- Bondy, B., Buettner, A., & Zill, P. (2006). **Genetics of suicide.** *Mol Psych*, 11, 336-351.
- Coryell, W., & Schlesser, M. (2001). **The dexamethasone suppression test and suicide prediction.** *Am J Psychiatry*, 158(5), 748-753.
- Coryell, W., & Schlesser, M. (2007). **Combined biological tests for suicide prediction.** *Psychiatry Res*, 150(2), 187-191.
- Coryell, W., Young, E., & Carroll, B. (2006). **Hyperactivity of the hypothalamic-pituitary-adrenal axis and mortality in major depressive disorder.** *Psychiatry Res*, 142(1), 99-104.
- Hasler, G., Drevets, W. C., Manji, H. K., & Charney, D. S. (2004). **Discovering endophenotypes for major depression.** *Neuropsychopharmacology*, 29(10), 1765-1781.
- Kendler, K. S. (2005). **"a gene for." The nature of gene action in psychiatric disorders.** *Am J Psychiatry*, 162(7), 1243-1252.
- Leonard, B. E. (2005). **The HPA and immune axes in stress: The involvement of the serotonergic system.** *Eur Psychiatry*, 20 Suppl 3, S302-306.
- Licinio, J., O'Kirwan, F., Irizarry, K., Merriman, B., Thakur, S., Jepson, R., et al. (2004). **Association of a corticotropin-releasing hormone receptor 1 haplotype and antidepressant treatment response in mexican-americans.** *Mol Psychiatry*, 9(12), 1075-1082.
- Liu, Z., Zhu, F., Wang, G., Xiao, Z., Tang, J., Liu, W., et al. (2007). **Association study of corticotropin-releasing hormone receptor1 gene polymorphisms and antidepressant response in major depressive disorders.** *Neurosci Lett*, 414(2), 155-158.
- Liu, Z., Zhu, F., Wang, G., Xiao, Z., Wang, H., Tang, J., et al. (2006). **Association of corticotropin-releasing hormone receptor1 gene SNP and haplotype with major depression.** *Neurosci Lett*, 404(3), 358-362.
- Mann, J. (2003). **The neurobiology of suicidal behavior.** *Nat Rev Genet*, 4, 819-828.
- Mann, J. J., Currier, D., Stanley, B., Oquendo, M. A., Amsel, L. V., & Ellis, S. P. (2006). **Can biological tests assist prediction of suicide in mood disorders?** *Int J Neuropsychopharmacol*, 9(4), 465-474.
- Meijer, O. C., & de Kloet, E. R. (1998). **Corticosterone and serotonergic neurotransmission in the hippocampus: Functional implications of central corticosteroid receptor diversity.** *Crit Rev Neurobiol*, 12(1-2), 1-20.
- Muller, N., & Schwarz, M. J. (2007). **The immune-mediated alteration of serotonin and glutamate: Towards an integrated view of depression.** *Mol Psychiatry*.
- Nemeroff, C. B., & Vale, W. W. (2005). **The neurobiology of depression: Inroads to treatment and new drug discovery.** *J Clin Psych*, 66 (suppl 7), 5-13.
- Nielsen, D. M. (2006). **Corticotropin-releasing factor type-1 receptor antagonists: The next class of antidepressants?** *Life Sci*, 78(9), 909-919.
- Papiol, S., Arias, B., Gasto, C., Gutierrez, B., Catalan, R., & Fananas, L. (2007). **Genetic variability at HPA axis in major depression and clinical response to antidepressant treatment.** *J Affect Disord*, 104, 83-90.
- Pfennig, A., Kunzel, H. E., Kern, N., Ising, M., Majer, M., Fuchs, B., et al. (2005). **Hypothalamus-pituitary-adrenal system regulation and suicidal behaviour in depression.** *Biol Psychiatry*, 57, 336-342.
- Roy, A., Pickar, D., Paul, S., Doran, A., Chrousos, G. P., & Gold, P. W. (1987). **CSF corticotropin-releasing hormone in depressed patients and normal control subjects.** *Am J Psychiatry*, 144(5), 641-645.
- Rujescu, D., Thalmeier, A., Moller, H. J., Bronisch, T., & Giegling, I. (2007). **Molecular genetic findings in suicidal behavior: What is beyond the serotonergic system?** *Arch Suicide Res*, 11(1), 17-40.
- Sah, D. W. (2006). **Therapeutic potential of rna interference for neurological disorders.** *Life Sci*, 79(19), 1773-1780.
- Swaab, D. F., Bao, A. M., & Lucasson, P. J. (2005). **The stress system in the human brain in depression and neurodegeneration.** *Ageing Res Rev*, 4, 141-194.
- Wasserman, D. (2001). **Suicide - an unnecessary death.** London: Martin Dunitz Publishers, Taylor & Francis Group.
- Wasserman, D. (2006). **Depression: The facts.** New York: Oxford University Press.
- Wasserman, D., Geijer, T., Sokolowski, M., Rozanov, V., & Wasserman, J. (2006). **Genetic variation in the hypothalamic pituitary adreno-cortical (HPA) axis regulatory factor, t-box19, and the angry/hostility personality trait.** *Genes Brain Behav*, 6(4), 321-328.
- Wasserman, D., Sokolowski, M., Rozanov, V., & Wasserman, J. (2007). **The CRHR1 gene - a marker for suicidality in depressed males exposed to low stress?** *Genes Brain Behav*, in press.
- Young, E. A. (2005). **Suicide and the hypothalamic-pituitary-adrenal axis.** *The Lancet*, 366, 959-960.