

24-hour cortisol profiles in sibpairs selected to be extremely concordant or discordant for depression

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Depression

Major depression reflects a combination of genetic vulnerability and environmental factors such as adverse life-events and lack of social support. The HPA-axis (hypothalamic-pituitary-adrenal axis) seems to be the central biological pathway on which these factors converge. This is supported by studies, mostly in clinical samples, showing elevation of the basal cortisol level, dexamethasone-mediated negative feedback resistance, increased cerebrospinal fluid levels of corticotropic releasing factor (CRF), and a blunted adrenocorticotrophic hormone (ACTH) response to challenge with exogenous CRF.

Genes for depression and cortisol?

One hypothesis states that the genetic susceptibility for depression derives in part from genes influencing HPA axis function. This was tested in the current study.

Repeated daytime saliva cortisol samples were obtained in selected families with sib pairs who were;

- 1) extremely concordant for low levels of the trait anxious depression
- 2) extremely concordant for high levels of anxious depression
- 3) extremely discordant for levels of anxious depression

We tested whether:

- Within families, siblings discordant for anxious depression are also discordant for daytime cortisol, such that the sibling with high anxious depression has the highest cortisol levels.
- Between families, siblings extremely concordant for high anxious depression (high family risk) have higher cortisol levels than siblings extremely discordant for low anxious depression (low family risk).

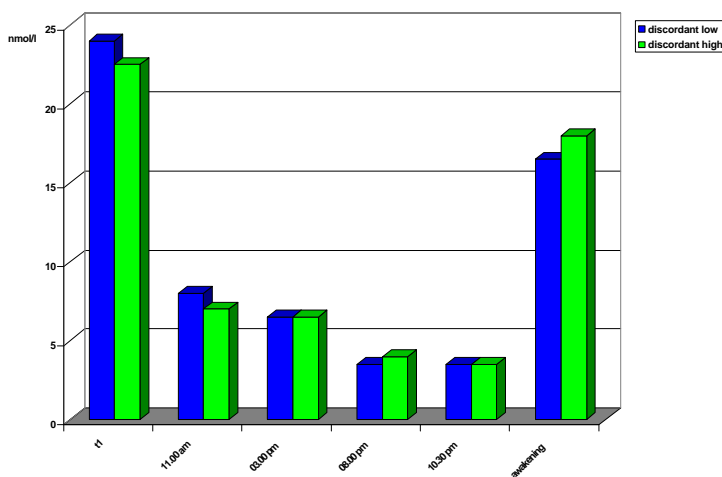
Selection of sib pairs

The subjects for this study were ascertained through the Netherlands Twin Register (NTR). Anxious depression was obtained in 3344 twin families from a normal population through longitudinal sampling of anxiety and depression in 1991, 1993 and 1997. Scales included the Beck Depression Inventory, the Spielberger Trait Anxiety Inventory (STAI) and the anxious/depression symptom scale of the Young Adult Self-Report (YASR). Sib-pairs were selected to be extreme on a factor score that optimally captures individual differences in the genetic contribution to the stability of anxiety and depression scores over time. This factor score correlated highly with the Composite International Diagnostic Interview (CIDI), a diagnostic psychiatric interview for the assessment of lifetime major depression, was obtained (Boomsma et al., 2000 *Twin Research*, vol 3(4), 323-334). Numbers in the study: low concordance N=58, high concordance N=61, discordant pairs N=43

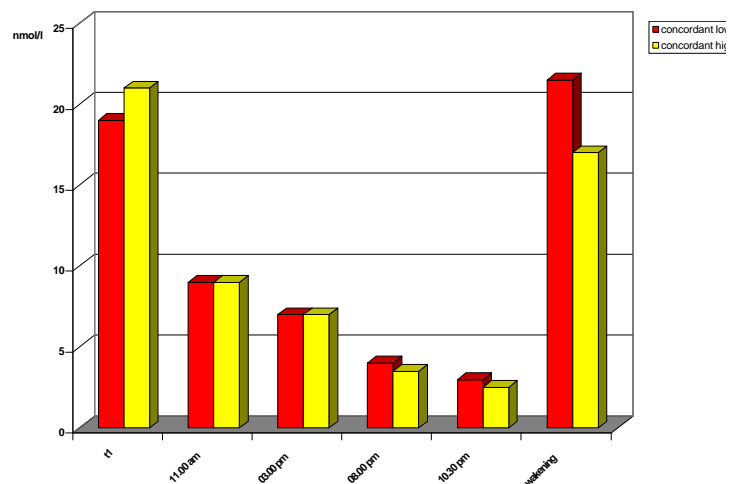
Cortisol sampling

Cortisol levels were measured in six saliva samples, using the Salivette method. The first sample was collected in the morning just after the instructions and the explanations on the protocol, and after the questionnaires on health and physical activity were administered. The other samples were collected at 11.00 a.m., 03.00 pm, 08.00 pm and 10.30 pm. For the final sample the subjects were instructed to collect it immediately after awakening, preferably while still in bed.

Cortisol profiles in the low and high sibling of discordant pairs



Average profiles of both siblings of concordant low and concordant high pairs



Summary and Discussion

- In extremely discordant pairs no differences were found daytime cortisol levels between the sibling with high anxious depression and the sibling with low anxious depression.
- Siblings from families with at least two offspring with high anxious depression did not have higher cortisol levels than siblings from families with at least two offspring concordant for low anxious depression.

These results do not support a common genetic factor underlying the trait anxious depression and daytime cortisol levels. It suggests that the high cortisol levels found in clinical depression reflect the chronic stress characterizing the acute phase of this disorder (e.g. hospitalization).