Pharmacological aspects of corticotrophinergic and vasopressinergic function tests for HPA axis activation

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Stellingen behorende tot het proefschrift

PHARMACOLOGICAL ASPECTS OF CORTICOTROPHINERGIC AND VASOPRESSINERGIC FUNCTION TESTS FOR HPA AXIS ACTIVATION

1 The major activatory HPA axis routes can be quantified in terms of adrenocorticotrpic hormone (ACTH) - and cortisol release using relatively specific pharmacological function tests, either by direct stimulation with the peripherally acting agents corticorelin (hCRH) and desmopressin (dDAVP) or by indirect stimulation with the centrally active drugs 5-hydroxytryptophan (5-HTP) and metoclopramide *(this thesis)*.

2 The combined 5-HTP/carbidopa/granisetron function test is a useful tool to quantify central serotonin-mediated corticotrophinergic HPA axis activation (this thesis). It can be used to study the integrity of the HPA axis in health and disease, and to examine the modification of HPA axis function by (pharmacological) treatments of (stress-related) psychiatric disorders.

3 It is plausible that serotonin-mediated HPA axis activation causes a temporary reduction of glutamate stores in the hypothalamus *(this thesis)*.

4 The dose at which dDAVP has few confounding cardiovascular (stress) effects is associated with too small and/or insufficiently specific activation to be useful as pharmacological function test to quantify vasopressinergic co-activation of the HPA-axis in healthy volunteers *(this thesis)*.

5 Vasopressinergic co-activation of the HPA axis is a dose-dependent function of ambient CRH concentrations or CRH_1-receptor activation, and can be mimicked pharmacologically by the concomitant administration of dDAVP and low doses hCRH *(this thesis)*.

6 Drugs that are applied as pharmacological function tests induce functional changes in (neuro)physiological systems. The magnitude of such changes is not only determined by the sensitivity of the system but also by the (plasma) concentrations of the function tests drug. The correct interpretation of effects of a function test therefore requires careful characterization of the pharmacokinetic properties of the function test drug.

7 Pharmacologically well-characterized function tests can be applied to examine whether HPA axis dysfunction is a pathogenetic factor in (stress-related) psychiatric disorders or merely an epiphenomenon of such psychopathology.

8 An important handicap of preclinical animal models that predict the clinical effects of novel drugs for the treatment of mood disorders, is that the majority of such models do not recognize the role of neurotransmitters other than the monoamines in the (dys)regulation of mood.

9 Although dolphins and whales are intellectually more superior laboratory animals than rodents, they are rather impractical and neither superior in human communication nor in demonstrating complex (behavioural) symptoms that underly psychiatric disorders in humans (adapted from *Striedter 2005, Principles of Brain Evolution*).

10 Superfluous bureaucracy involved in the developmental process of novel drugs often discourages fruitful collaboration between the (result driven) pharma industry and the (traditionally reserved) academia.

11 Every psychiatrist that is confronted with a therapy resistent patient, should be able to consider basic clinical pharmacological principles in discerning true therapy resistance from potentially reversible pharmacological treatment complications.

12 If you talk to a man in a language he understands, that goes to his head. If you talk to him empathically, that goes to his head all the same but activates the necessary neuronal circuits for psychotherapy to be effective (adapted from *Nelson Rolihlahla Mandela*).