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# Metoclopramide as pharmacological tool to assess vasopressinergic co-activation of the hypothalamus–pituitary–adrenal (HPA) axis: A study in healthy volunteers

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**Abstract**

The synthetic vasopressin (AVP) analogue desmopressin (dDAVP) has been used as pharmacological function test to quantify vasopressinergic co-activation of the hypothalamus–pituitary–adrenal (HPA) axis in the past. Such exogenous vasopressinergic stimulation may induce confounding cardiovascular, pro-coagulatory and anti-diuretic effects and low endogenous corticotrophin-releasing-hormone (CRH) levels may limit its potential to reliably assess co-activation. Alternatively, the dopamine-2-(D2)-antagonist metoclopramide is believed to induce co-activation indirectly by releasing endogenous AVP. We investigated this indirect co-activation with metoclopramide under conditions of low and enhanced endogenous CRH release in healthy volunteers. A randomized, double-blind, placebo-controlled, four-way crossover study was performed in 12 healthy males. CRH release was induced by administering an oral 5-hydroxytryptophan (5-HTP) 200 mg function test. Co-activation was investigated by administering metoclopramide 10 mg intravenously around the expected maximal effect of 5-HTP. The neuroendocrine effects were compared to those of metoclopramide alone, the 5-HTP test alone and matching placebo. Metoclopramide safely induced HPA-axis activation by itself, and potently synergized 5-HTP-induced corticotrophinergic activation of the HPA axis. These findings are indicative of vasopressinergic co-activation and suggest a role for metoclopramide as a practical

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function test for co-activation of the HPA axis. However, its application will be hampered pending clarification of the exact pharmacological mechanism by which metoclopramide induces co-activation of the HPA axis.
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## 1. Introduction

Corticotrophin-releasing hormone (CRH) and arginine-vasopressin (AVP) are the major neuropeptide activators of the hypothalamus–pituitary–adrenal (HPA) axis (Aguilera and Rabadan-Diehl, 2000; Ring, 2005; Scott and Dinan, 1998). Under physiological circumstances, CRH acts as a major neuroendocrine secretagogue that induces corticotrophinergic HPA activation via pituitary $CRH_1$ receptors ($CRH_1$), while AVP by itself has weak neuroendocrine properties and induces vasopressinergic co-activation of the HPA at pituitary vasopressin 3 receptors ($V_3$, also referred to as $V_{1b}$ receptor) (Ring, 2005; Scott and Dinan, 1998; Scott and Dinan, 2002). Following acute stress, AVP releases adrenocorticotrophic hormone (ACTH) synergistically in the presence of increased levels of CRH (DeBold et al., 1984; Favrod-Coune et al., 1993; Lamberts et al., 1984). During chronic stress, either increased AVP synthesis and/or release, increased $V_3$ responsivity and/or expression (Goekoop and Wiegant, 2009), genetic polymorphisms of the $V_3$-receptor (Dempster et al., 2007) or a combination of these factors is hypothesized to lead to chronic HPA hyperactivity (Aguilera and Rabadan-Diehl, 2000; Volpi et al., 2004). In this context, sustained vasopressinergic co-activation has been implicated in stress-related psychopathology (Dinan et al., 2004; Dinan and Scott, 2005; Holsboer, 1983; Holsboer et al., 1984b; Volpi et al., 2004). A pharmacological function test that quantifies vasopressinergic co-activation would therefore be a useful tool to study this functional component of the HPA axis in health and disease, and during treatments directed at the vasopressinergic system.

The synthetic analogue of AVP, desmopressin (dDAVP) is frequently applied as pharmacological function test for vasopressinergic co-activation (Dinan et al., 1999; Dinan et al., 2004). It stimulates the $V_3$ receptor directly in the presence of (endogenous) CRH, inducing pituitary ACTH and subsequent adrenal cortisol release. Most experiments with dDAVP in healthy volunteers occur in the mid-morning when HPA-axis activity and endogenous CRH levels are relatively low. Since AVP acts in synergy with CRH, 10 μg dDAVP induces small and (frequently) variable co-activation under low CRH activity (Dinan et al., 1999; Dinan et al., 2004; Jacobs et al., 2010b). Too small or too variable responses limit the test's informative value and would not allow for an accurate assessment of conditions or treatments that modulate vasopressinergic co-activation. Recent studies have shown that doses higher than 10 μg dDAVP alone may not produce much more ACTH- or cortisol release during baseline conditions (Jacobs et al., 2010b). Moreover, higher dDAVP doses may cause (confounding) cardiovascular, pro-coagulatory and anti-diuretic effects which would limit its tolerability and applicability (Jacobs et al., 2010b). Alternative ways of inducing informative vasopressinergic co-activation therefore need to be explored.

One approach would be to stimulate endogenous release of AVP instead of exogenous stimulation of $V_3$ receptors. The $D_2$-receptor antagonist antiemetic metoclopramide has been shown to activate the HPA axis (Chiodera et al., 1986; Seki et al., 1997; Walsh et al., 2005). It is hypothesized to produce vasopressinergic co-activation by endogenously releasing AVP from the pituitary and/or hypothalamus, through a hitherto unclear pharmacological mechanism (Chiodera et al., 1986; Nomura et al., 1984). If this were the case, metoclopramide would not affect CRH levels and would induce small neuroendocrine responses that are comparable to those achieved by dDAVP under low CRH activity. Stimulation of the CRH system by exogenous administration of human corticotrophic release hormone (hCRH) induces considerably greater HPA-axis activation (Dinan et al., 1999; Holsboer, 1983; Holsboer et al., 1984a; von Bardeleben and Holsboer, 1988). Alternatively, serotonergic (precursor) agents can be used as endogenous corticotrophinergic stimulants of the HPA axis (Dinan et al., 1999; Gijsman et al., 1998; Gijsman et al., 2002; Smarius et al., 2008). A serotonergic function test consisting of 5-hydroxytryptophan (5-HTP) has been developed for this purpose (Jacobs et al., 2010a). 5-HTP is the direct precursor of serotonin (5-HT) and is centrally converted into 5-HT. Enhanced 5-HT release stimulates CRH release via postsynaptic $5\text{-}HT_{2A}$ or $5\text{-}HT_{2C}$ receptors in the paraventricular nucleus (PVN) of the hypothalamus (Gartside and Cowen, 1990; Jorgensen et al., 2002). The neuroendocrine response associated with the endogenous release of CRH (by administering 5-HTP) is therefore expected to be synergized by endogenously released AVP (with metoclopramide). Moreover, such an effect would be an (indirect) indication of vasopressinergic co-activation of the HPA axis with metoclopramide.

We examined metoclopramide's effect on neuroendocrine HPA-axis activation under physiological circumstances (by administering metoclopramide alone) and under enhanced CRH-mediated activation of the HPA axis (by administering the 5-HTP function test followed by metoclopramide) in healthy male volunteers.

## 2. Experimental procedures

### 2.1. Study design

The study protocol was approved by the Medical Ethics Committee of Leiden University Medical Centre (LUMC) and performed according to Good Clinical Practice and International Conference on Harmonisation (GCP-ICH) guidelines. A randomized, double-blind, double-dummy placebo-controlled, four-way crossover trial was performed in 12 healthy volunteers.

### 2.2. Main outcome measures

The main pharmacodynamic (PD) outcome measures were the neuroendocrine effects (serum ACTH, cortisol, prolactin and AVP) of 10 mg metoclopramide, the 200 mg 5-HTP function test, and 10 mg metoclopramide combined with the 200 mg 5-HTP function test. Also, adverse events (AEs) were recorded to assess the safety

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