

Corticotropin-Releasing Hormone Receptor 1 Antagonist With or Without Corticotropin-Releasing Hormone Receptor 2 Remain Promising in Relieving Human Acute Psychological Stress and Related Intestinal Hyperpermeability

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ABSTRACT

Corticotropin-releasing hormone (CRH) has clinical relevant to stress, feeding behavior, gut motility and immunity. Emerging evidence indicates that two CRH receptor subtypes, receptor 1 (CRH1-R) and 2 (CRH2-R), play pivotal roles in the regulation of these biological functions induced by CRH, depending on which receptor subtypes to be activated. Manipulating and balancing at CRH1-R and CRH2-R has become a novel concept to treat stress-related disorders and gut dysfunction, such as psychological stress and related intestinal hyperpermeability.

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Key words: Corticotropin-releasing hormone; Intestinal hyperpermeability; Receptor; Stress

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EDITORIAL

A recent interesting article by Vanuytsel et al^[1] (Vanuytsel *et al*, 2014) describing psychological stress and corticotropin-releasing hormone (CRH) to increase intestinal permeability in humans through a mast cell-dependent mechanism. The authors concluded that public speech rather than electroshock induced intestinal hyperpermeability. Although both public speech and electroshock increased State-Trait Anxiety Inventory (STAI) score, only public speech but not electroshock stimulated the increase of salivary cortisol level, which reflexes the activation of the hypothalamic-pituitary-adrenal (HPA) axis. It is very interesting to know how electroshock induced stress without affecting the HPA axis. We doubt that the intensity of electroshock plays a role in this difference.

The authors further demonstrated that public speech not only elicited stress, activated HPA axis, but also increased intestinal permeability. In addition, intravenous administration of CRH reproduced stress-induced increases in salivary cortisol and intestinal permeability, but not STAI score. In this study, exogenous CRH was used to mimic the stressful conditions. We are curious about why intravenously-injected CRH stimulated HPA axis (salivary cortisol was increased) without eliciting any anxiety in man. One of the explanations is peripheral CRH does not mimic perfectly the psychological stress response and that of central administration of CRH. In this paper, the authors did not mention the plasma concentrations of adrenocorticotrophic hormone, i.e. the downstream

mediator of CRH and upstream of cortisol. The measurement of plasma adrenocorticotrophic hormone can give us further information. The level of salivary cortisol may reflect both cortisol and salivary secretory capacity, but the latter of which may be affected by stress and sympathetic nervous system.

The results that the intestinal hyperpermeability, but not salivary cortisol concentrations (and/or STAI score), induced by public speech and exogenous CRH was blocked by mast cell stabilizer sodium cromoglycate, may reveal the superiority of CRH receptor antagonists to mast cell blockers in reversing central neuroendocrinological and peripheral gut mucosal barrier dysfunctions (Chen *et al*^[2], 2014). Neuropeptides tend to produce different neurobiological actions depending on which receptor subtype they activate. CRH receptor 1 (CRH₁-R) antagonist has been shown to attenuate hippocampal noradrenaline release, visceral perception, adrenocorticotrophic hormone release, and anxiety in a rodent model (Saito *et al*^[3], 2005). On the other hand, CRH receptor 2 (CRH₂-R) has been demonstrated to induce anxiolytic response via phosphorylation of the transcription factor cAMP response element-binding protein (Creb) but not activation of HPA (Kishimoto *et al*^[4], 2000). Furthermore, CRH₁-R has been identified on the cell surface of human intestinal mucosal mast cells, and CRH is reported to activate CD14⁺ cells to produce tumor necrosis factor- α and induce endothelial barrier dysfunction (Song *et al*^[5], 2013). Using respective agonists and/or antagonists of CRH₁-R and CRH₂-R in exploring human acute psychological stress and related alteration of intestinal permeability becomes a very intriguing topic.

CONCLUSION

In conclusion, differentially nibbling CRH₁-R and CRH₂-R remains promising for the management of human acute psychological stress and related intestinal hyperpermeability. The collective evidence can provide useful implications for the future treatment and functional gastrointestinal disorders, such as irritable bowel syndrome.

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CONFLICT OF INTERESTS

The Author has no conflicts of interest to declare.

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