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Review

The cellular mechanisms of the antiemetic action of dexamethasone and related glucocorticoids against vomiting

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ABSTRACT

Glucocorticoids, used primarily as anti-allergic and anti-inflammatory drugs, are also effective, alone or combined with other antiemetics, for preventing nausea and vomiting. Dexamethasone, one of the glucocorticoids, has been suggested as a first-line drug for preventing low-level emetogenic chemotherapy- and radiotherapy-induced nausea and vomiting, and in patients with only one or two risks for postoperative nausea and vomiting (PONV). Dexamethasone combined with 5-HT_3 or tachykinin NK_1 antagonists is also suggested for higher-level emetogenic chemotherapy and radiotherapy and for patients at high risk for PONV. Glucocorticoids may act via the following mechanisms: (1) anti-inflammatory effect; (2) direct central action at the solitary tract nucleus, (3) interaction with the neurotransmitter serotonin, and receptor proteins tachykinin NK_1 and NK_2, alpha-adrenaline, etc.; (4) maintaining the normal physiological functions of organs and systems; (5) regulation of the hypothalamic-pituitary-adrenal axis; and (6) reducing pain and the concomitant use of opioids, which in turn reduces opioid-related nausea and vomiting.

Contents

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1. Introduction

Dexamethasone, like other synthetic glucocorticoids (e.g., prednisolone, methylprednisolone), is used primarily as an anti-allergic and anti-inflammatory drug (Hornby, 2001). More than 30 years ago, dexamethasone was also reported to be effective for preventing chemotherapy-induced nausea and vomiting (CINV) (Aapro and Alberts, 1981; Markman et al., 1984). Thereafter, dexamethasone and related glucocorticoids were shown to help prevent radiotherapy-induced nausea and vomiting (RINV) (Kirkbride et al., 2000) and postoperative nausea and vomiting (PONV) (Fujii et al., 1997; Wang et al., 1999a, 1999b). Several major international antiemetic guidelines, viz., the Multinational Association for Supportive Care in Cancer (MASCC)/European Society of Medical Oncology (ESMO) (Feyer et al., 2011), the American Society of Clinical Oncology (ASCO) (Basch et al., 2011), and the National Comprehensive Cancer Network (NCCN) (Jordan et al., 2007), recommend dexamethasone, a commonly used glucocorticoid, for preventing CINV and RINV, and the Society of Ambulatory Anesthesia (SAMBA) (Gan et al., 2007) also recommend dexamethasone for preventing PONV. Dexamethasone is as effective (MASCC level of confidence: moderate to high), for preventing both acute and delayed CINV as are the other two groups of commonly used antiemetics, i.e., 5-hydroxytryptamine 3 (5-HT_3) receptor antagonists (e.g., ondansetron), and tachykinin NK_1 receptor antagonists (e.g., aprepitant) (Roila et al., 2006). All three groups of drugs are considered first-line drugs for preventing CINV (Grunberg, 2007). However, for patients with a high risk for emesis, a combination of drugs from these three groups is most beneficial (Basch et al., 2011; Roila et al., 2010). For preventing RINV, both dexamethasone and 5-HT_3 antagonists are the first-line drugs (Feyer et al., 2011), and for preventing PONV, dexamethasone is effective alone for low-risk patients, and for moderate-to-high-risk patients when combined with other antiemetics (Kim et al., 2007; Leksowski et al., 2006; Szarvas et al., 2003). Dexamethasone, ondansetron, and droperidol have each reduced the risk of PONV by about 26 percent (Apfel et al., 2004).

However, glucocorticoids have only a limited effect on preventing nausea and vomiting induced by potent emetics such as apomorphine (Axelsson et al., 2006) or copper sulfate (Rudd et al., 1996). Moreover, glucocorticoids are effective only for preventing nausea and vomiting, not for treating established nausea and vomiting; therefore, they are not suggested for treating the latter (Kazemi-Kjellberg et al., 2001).

2. Basic pharmacologic actions of glucocorticoids

2.1. General pharmacology

Corticosteroids, secreted from the adrenal cortex, are divided into two classes: glucocorticoid and mineralocorticoid (Streeten, 1976). Only the glucocorticoids are antiemetics (Basch et al., 2011; Gan, 2007; Jordan et al., 2007; Rich et al., 1980; Roila et al., 2010; Scuderi, 2003). While encountering physical insults such as inflammation, infection, pain, or psychological such as emotional stress, the hypothalamic-pituitary-adrenal (HPA) axis is activated. Firstly, these stimuli excite the hypothalamus, which responds by liberating corticotropin releasing hormone (CRH). Secondly, CRH acts on the anterior pituitary to induce the synthesis and release of adrenocorticotropic hormone (ACTH). Thirdly, ACTH in turn stimulates the adrenal cortex to release glucocorticoids such as cortisol. Contrarily, glucocorticoids can exert a negative feedback inhibition of the HPA axis by repressing CRH and ACTH expression (Newton, 2000). Cortisol is the only natural glucocorticoid hormone, but all the others (e.g., prednisolone, methylprednisolone, triamcinolone, betamethasone, and dexamethasone) are synthetic (Streeten, 1976). The clinical efficacy of synthetic glucocorticoids arises from their ability to mimic natural glucocorticosteroids.

In general, glucocorticoids have two major functions: [i] to modulate the metabolism of carbohydrates, proteins, fat, etc. and [ii] to preserve the functions of the cardiovascular, immune, renal, muscular, endocrine, and nervous systems (Streeten, 1976). When the secretion of glucocorticoid is insufficient, these functions will either decline or become imbalanced (Hornby, 2001). Glucocorticoids are necessary during stress, and a glucocorticoid deficiency may cause nausea and vomiting (Hursti et al., 1993; Kageyama, 2000; Oelkers, 1996).

2.2. Glucocorticoid actions on glucocorticoid receptors

Glucocorticoids produce their effects through their actions on the intracellular glucocorticoid receptors, which exist in virtually all cells, to directly or indirectly regulate the transcription of certain target genes (Barnes, 1998; Buckbinder and Robinson, 2002; Morimoto et al., 1996; Newton and Holden, 2007). The target gene can be transactivated or transrepressed (Table 1) (Barnes and Adcock, 2003; Newton, 2000; Newton and Holden, 2007). The number of genes per cell directly regulated by glucocorticoids is estimated to be between 10 and 100, and some others are indirectly regulated (Barnes, 1998). In direct regulation, the glucocorticoid receptor, after the glucocorticoid has bound with it, moves into the nucleus and then binds to a short DNA sequence, called a glucocorticoid-response element (GRE), in the 5′-upstream premotor region of the GRE. This binding changes the rate of transcription, which either induces (transactivation) or inhibits (transpression) the response genes (Barnes, 1998; Buckbinder and Robinson, 2002; Lu et al., 2006; Rhen and Cidlowski, 2005). Transactivation is responsible for numerous adverse effects of glucocorticoids; transrepression is responsible for many of the clinically desirable anti-inflammatory and immunosuppressive effects of glucocorticoids. Glucocorticoids may also indirectly regulate some other genes by acting on transcription factors without the DNA binding to the GRE, e.g., activator protein 1 (AP-1), nuclear factor (NF)-κB, tumor necrosis factor (TNF)-α, and phorbol ester, etc. (Barnes, 1998; McKay and Cidlowski, 1999; Newton, 2000). Because this effect does not require the glucocorticoid receptor to directly bind to DNA, the term "tethering GRE" is often used to describe these elements. This phenomenon was first described for AP-1 and was thought to involve direct protein–protein interactions between the glucocorticoid receptor and AP-1. Similar to AP-1, glucocorticoids are able to repress the transcriptional activation of NF-κB via a direct interaction of the glucocorticoid receptor with NF-κB (Newton, 2000). All these transcription factors are critical for regulating the expression of many inflammatory and immune genes (Barnes, 1998; Buckbinder and Robinson, 2002; Lu et al., 2006; Rhen and Cidlowski, 2005). In addition to regulating genes, glucocorticoids also exert their effects via rapid, nongenomic mechanisms that can be classified as involving nonspecific interactions of glucocorticoids with cellular membranes, nongenomic effects that are mediated by cytosolic glucocorticoid receptors, or specific interactions with membrane-bound glucocorticoid receptors (Ayroldi et al., 2012; Buttgereit, 2000). For example,