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Review

A multi-hit endocrine model of intrinsic adult-onset asthma

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Abstract

Epidemiological studies indicate that adult-onset asthma is initiated by stress (anxiety and depression), obesity and menopause. Ironically, despite our understanding of the various stressors that promote chronic adult-onset asthma, most of which are known to elevate cortisol production via the hypothalamic–pituitary–adrenal (HPA) axis, inhaled and systemic corticosteroids are the mainstay for the treatment of chronic asthma. This implicates other endocrine or cellular changes independent of cortisol synthesis in non-allergic adult-onset asthma. The mechanism by which corticosteroids are thought to modulate bronchial tone in relieving asthma is via corticosteroid-responsive genes that increase PGE_2 and cAMP production which promote muscle relaxation. Therefore, any physiological condition that suppresses intracellular PGE_2 and cAMP production would counter cortisol-induced muscle relaxation and potentially trigger non-allergic adult-onset asthma. Stress, obesity and menopause act on three interrelated endocrine pathways, the serotonergic, leptinergic and hypothalamic pathways, all of which operate through receptors to modulate cAMP and Ca^{2+} metabolism in smooth muscle cells (SMCs). We propose that the level of SMC cAMP, as determined by overall signaling through corticosteroid receptors, leptin receptors and the GPCRs of the HPG and serotonergic pathways, will regulate bronchial tone (i.e. the 'Multi-Hit Endocrine Model of Adult-Onset Asthma'). Thus, decreases in HPG (menopause) and serotonergic (depression) signaling and increases in leptinergic (obesity) signaling relative to HPA signaling would decrease cellular SMC cAMP and promote muscle contraction. This model can explain the discrepant epidemiological data associating stress, obesity, depression and menopause with adult-onset asthma and is supported by basic and clinical data. Treatment of depressed or menopausal asthmatics with selective serotonin reuptake inhibitors or hormone replacement therapy, respectively, alleviates bronchoconstriction. Future therapeutic strategies might therefore target the serotonergic, leptinergic and hypothalamic pathways in regulating cellular cAMP production and bronchoconstriction for the treatment of adult-onset asthma.
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Keywords: Adult-onset asthma; Menopause; Obesity; Depression; Bronchial tone; cAMP; Muscle contraction; Serotonin; Leptin; Hypothalamic–pituitary–gonadal axis; Hypothalamic–pituitary–adrenal axis; G protein-coupled receptors; Prostaglandins; Calcium; Gonadotropin-releasing hormone; Luteinizing hormone; 17β-Estradiol; Menstrual cycle; Conjugated equine estrogens; Gonadotropin-releasing hormone receptor I; Leptin receptor

Abbreviations: cAMP, cyclic adenosine monophospate; CEEs, conjugated equine estrogens; ER, estrogen receptor; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; GPCRs, G protein-coupled receptors; HPA, hypothalamic–pituitary–adrenal; HPG, hypothalamic–pituitary–gonadal; 5-HT, 5-hydroxytryptamine, serotonin; HRT, hormone replacement therapy; LH, luteinizing hormone; MDD, major depressive disorder; MLCK, myosin light chain kinase; PGE_2, prostaglandin E_2; ObR, leptin receptor; SMC, smooth muscle cell; SSRI, selective serotonin reuptake inhibitor.

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1. Introduction

Asthma is a chronic disease of the lungs in which the airways become blocked or narrowed causing breathing difficulty. Asthma involves a nonspecific bronchial hyper-responsiveness, increased maximal airway narrowing, deficient response of the airways to deep inspiration, progressive loss of airway distensibility, and a loss of lung elastic recoil. Bronchial constriction induced by smooth muscle cell (SMC) contraction is therefore a key to understanding asthma.

This chronic disease affects nearly 20 million Americans (Centers for Disease Control, 2001) and is commonly divided into two types: allergic (extrinsic) asthma and non-allergic (intrinsic) asthma. The symptoms of allergic and non-allergic asthma are the same (coughing, wheezing, shortness of breath or rapid breathing, and chest tightness). Unlike allergic asthma which is triggered by inhaled allergens, non-allergic (intrinsic) asthma is triggered by factors associated with stress, including anxiety, depression, exercise, menopause, obesity, cold air, dry air, hyperventilation, smoke, viruses, infections or other irritants, and the immune system does not appear to be centrally involved.

2. Adult-onset asthma

Although ~3% or more of adult-onset asthma is triggered by allergies, the remaining cases appear to be of the non-allergic (intrinsic) type of asthma. A key difference between early onset and adult-onset asthma is that unlike children who often experience intermittent asthma symptoms in response to allergy triggers or respiratory infections, adults with newly diagnosed asthma generally have *persistent* symptoms. This suggests that late-onset asthma is triggered by a *chronic systemic* change rather than by the exposure to an allergen.

3. Endocrine systems affected by stress

Non-allergic adult-onset asthma appears to result from the various stresses mentioned above. Ironically, despite our understanding of the various stressors that promote chronic adult-onset asthma, most of which are known to *elevate* cortisol production via the hypothalamic–pituitary–adrenal (HPA) axis, inhaled and systemic corticosteroids are in fact the mainstay for the *treatment* of chronic asthma (Chrousos and Harris, 1998a,b). This suggests that increased cortisol synthesis and secretion *per se* is not the trigger for non-allergic asthma, but that other stress-induced endocrine or cellular changes induce non-allergic adult-onset asthma. Other endocrine systems impacted by stress include the hypothalamic–pituitary–gonadal (HPG) axis and leptinergic and serotonergic systems. Stresses, such as those associated with aging, lead to an increase in the adrenal secretion of cortisol that suppresses serum reproductive hormones of the HPG axis (reviewed in Bowen and Atwood, 2004), including gonadotropin-releasing hormone (GnRH), the gonadotropins and sex steroids. Stress and menopause also induce reductions in sex hormones (reviewed in Atwood and Bowen, 2007) which can lead to centralized obesity and an elevation in serum leptin (Rosenbaum et al., 1996). Obesity is directly correlated with serum leptin concentration (e.g. Ma et al., 1996). Stress (anxiety/depression) also modulates intracellular serotonin (5-hydroxytryptamine; 5-HT) levels (Shimizu et al., 1992).

I will discuss these endocrine systems (HPA, HPG, serotonergic and leptinergic) with relation to asthma, before describing potential interactions important in understanding non-allergic adult-onset asthma.

3.1. HPA axis and asthma

Following exposure to stress, cortisol is secreted from the adrenal cortex under the control of the HPA axis. Central in the regulation of the HPA axis is a two tiered corticosteroid-receptor system, comprised of high and low affinity receptors, the mineralocorticoid receptor and the glucocorticoid receptor, respectively. In addition, these corticosteroid receptors mediate the effects of cortisol during stress on both central and peripheral targets. Cortisol modulates gene-expression of corticosteroid-responsive genes, with the effect lasting from hours to days. Cortisol is known to increase PGE_2 and cAMP production leading to muscle relaxation. This is the mechanism by which corticosteroids are thought to modulate bronchial tone in relieving asthma (Chrousos and Harris, 1998a,b).

Interestingly, cortisol levels are *elevated* during aging, a time when the incidence of adult-onset asthma *increases*. These results indicate that while chronic corticosteroid treatment may suppress asthma, factors that suppress intracellular PGE_2 and cAMP production could counter cortisol-induced muscle relaxation and potentially trigger non-allergic adult-onset asthma.

3.2. Menopause/andropause, the HPG axis and asthma

The HPG axis is composed of centrally produced hormones including GnRH from the hypothalamus and gonadotropins, luteinizing hormone (LH) and follicule-stimulating hormone (FSH), from the pituitary, and peripherally produced hormones including estrogens, progestogens, androgens and inhibins that are primarily of gonadal origin, and activins and follistatin produced in all tissues including the gonads (Carr, 1998). There is mounting evidence that both endogenous and exogenous estrogen and progesterone can affect lung function across the life span in women (e.g. Haggerty et al., 2003). Most notable is the differential incidence of asthma over the menstrual cycle; premenopausal women experience decreases in pulmonary function and increases in asthma exacerbations and hospitalizations during the premenstrual and menstrual phases (when serum 17β-estradiol, progesterone, GnRH and LH/FSH levels are lowest; Skobeloff et al., 1996; Chandler et al., 1997; Prudhomme, 1999; Ensom et al., 2003a,b; Dziedziczko et al., 2004). Oral contraceptives are associated with improved pulmonary function, peak expiratory flows, a decrease in asthma exacerbation and a decrease in corticosteroid requirement (Chandler et al., 1997; Ensom et al., 2003b; Dziedziczko et al., 2004) independent of beta 2-receptors (Chandler et al., 1997). Other reports however have shown falls in peak respiratory flow rate that coincide with ovulation, and dramatic improvement in respiratory flow in these individuals with oral contraceptives (Matsuo et al., 1999). Recently, estrogen receptor (ER) 1 polymorphisms have been associated with airway hyper-responsiveness and lung function decline (Dijkstra et al., 2006) while ERα deficient mice display spontaneous airway hyper-responsiveness (Carey et al., 2007). Together these findings suggest that sex hormone signaling regulates bronchial tone, although the timing of asthma-onset may be regulated by other factors.

In the peri- and post-menopausal period, asthma may worsen in women with prior disease. At this time, there is a dramatic decrease in sex steroid and inhibin synthesis, and this loss of hypothalamic feedback inhibition is responsible for the unopposed elevation of GnRH and gonadotropins following ovarian senescence (Fig. 1; Carr, 1998). Most researchers examining the effects of menopause on asthma have focused on the sex steroids (17β-estradiol, testosterone and progesterone). The rate of disease onset during this period is higher than in other age groups (Prudhomme, 1999). Unlike the consistent results obtained with oral contraceptives in younger women, hormone replacement therapy (HRT) has been shown to have similar beneficial effects (Mueller et al., 2003), no effect, or a

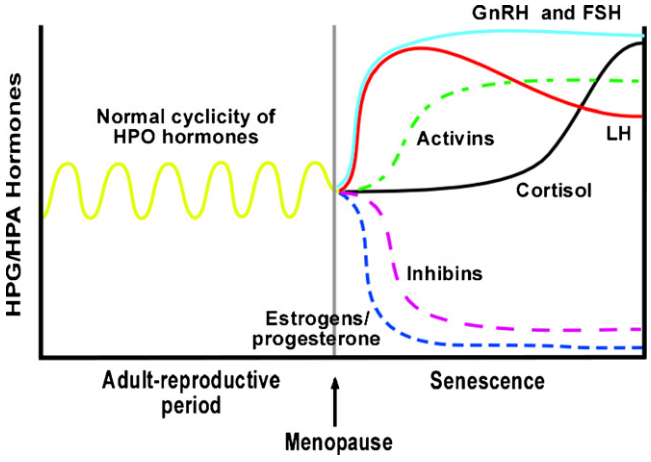

Fig. 1. HPG and HPA hormonal profiles following menopause and during andropause. Reproductive changes result in a net change in cellular signaling induced by the increase in serum concentrations of GnRH, LH and activin and decrease in serum sex steroids. Serum LH, but not FSH, declines to ~50% peak values in the very old (80–100 years), perhaps as a response to increasing serum concentrations of prolactin and estrone. The concentration of serum cortisol also progressively increases after ~65–70 years of age to high levels.

negative effect (Hepburn et al., 2001). Indeed, some epidemiological studies indicate that postmenopausal hormone use is associated with an increased risk of developing asthma (Prudhomme, 1999; Troisi et al., 1995; Barr and Camargo, 2004; Barr et al., 2004a). This discrepancy in the protection offered by oral contraceptives and HRT may be explained by the different estrogens/progestagens used for oral contraception (17β-estradiol/progesterone) versus HRT (mostly conjugated equine estrogens (CEEs)/medroxyprogesterone). The use of unnatural estrogens/progestogens (i.e. CEEs/medroxyprogesterone) in women has been shown to result in altered cellular signaling (see Turgeon et al., 2004 for a review). In this context, transdermal application of 17β-estradiol every day of the menstrual cycle in asthmatic post-menopausal women over a 6 month period lead to normalized serum 17β-estradiol concentrations and diminished symptoms of asthma (Kos-Kudla et al., 2000). These positive affects of estrogen also could be explained by concomitant changes in GnRH and gonadotropins, since HRT feedback on the hypothalamus suppresses serum concentrations of these hormones (Carr, 1998). Importantly, we and others have discovered that, like the sex steroids, GnRH, LH and activin receptors are present and functional on all tissues of the body examined (Vadakkadath Meethal and Atwood, 2005), indicating that any change in serum hormones and thus signaling would impact all tissues, including the lungs. Sex steroid receptors, LH/hCG receptor protein and GnRH mRNA have been identified in the lung (Tieva et al., 2001; Abdallah et al., 2004), although their function remains unknown. GnRH and GnRH receptor mRNA also is expressed in SMCs (Chegini et al., 1996).

Taken together, these studies indicate that HPG hormones modify airway responsiveness. However, the discrepant data regarding the menstrual cycle, and the effects of sex steroid replacement on asthma, suggest that other factors impact upon whether an individual will develop asthma.

3.3. Major depressive disorder, the serotonergic pathway and asthma

Another hormonal system that is altered by stress is the serotonergic system. I made this observation from a close relative with adult-onset asthma during a stressful period of their life, during which time they were anxious and depressed and required chronic corticosteroid treatment to suppress asthma. Treatment of the depression finally led to the resolution of the chronic asthma. This case study suggested that, like the more recent epidemiological and clinical data linking asthma with depression (discussed below), that serotonergic pathways might play a role in adult-onset asthma.

Major depressive disorder (MDD) is a common, severe and disabling illness with a 17.1% lifetime prevalence in the general population (Kessler et al., 1994). Interestingly, depressive symptoms and depressive disorders appear to be very common in asthma patients (for a review see Zielinski and Brown, 2003). Lifetime rates of MDD of up to 47% have been reported in clinical samples of patients with asthma (Nejtek et al., 2001). In this context, greater depressive symptom severity has been reported in asthma patients than in healthy controls and other medically ill populations (e.g. rheumatoid arthritis, ulcerative colitis, hypertension) (Lyketsos et al., 1987).

Clinical observations support the idea that chronic changes in 5-HT production promote asthma. Most recently, a 12-week, randomized, double-blind, parallel-group, placebo controlled trial of citalopram, a selective serotonin reuptake inhibitor (SSRI), conducted in 90 depressed outpatients with asthma indicated this treatment reduced depressive symptoms and asthma (Brown et al., 2005). Systemic corticosteroid use, an important measure of severe asthma exacerbations, was 4-fold lower in the citalopram group during the trial. Despite the well documented association of asthma with depression, this is the only study of anti-depressants (SSRI's) in the treatment of asthma. Conversely, there is the unfortunate case report of a young woman who induced an acute asthma attack with an overdose of the SSRI, sertraline hydrochloride (Zoloft; 620 ng/ml serum level; Carson et al., 2000). Autopsy indicated the suicide was a result of an asthma attack, presumably due to altered 5-HT concentrations induced by the overdose and triggering acute bronchoconstriction (see below). Further evidence supporting a role of 5-HT in asthma is that 5-HT plasma levels are elevated in symptomatic asthmatic patients when compared to nonasthmatics (Lechin et al., 1996). Although the exact mechanism of action of SSRI's in modulating mood is unclear, these results indicate the serotonergic pathway can regulate bronchial tone and can induce asthma.

3.4. Obesity, the leptinergic pathway and asthma

Obesity increases the prevalence, incidence, and possibly the severity of asthma, while weight loss in the obese improves asthma outcomes (see Shore and Fredberg, 2005 for a review). Obesity also influences asthma control and

the response to standard asthma therapeutics; obesity appears to be particularly important for severe asthma because obese or overweight subjects account for 75% of emergency department visits for asthma (Thomson et al., 2003). As reviewed by Shore and Fredberg (2005), longitudinal studies indicate that obesity antedates asthma and that the relative risk of incident asthma increases with increasing obesity (Camargo et al., 1999; Guerra et al., 2004). Furthermore, morbidly obese asthmatic subjects studied after weight loss demonstrate decreased severity and symptoms of asthma (Aaron et al., 2004). Therefore, obesity appears to predispose toward asthma and is a risk factor for airway hyper-responsiveness (Chinn et al., 2002; Celedon et al., 2001). Although both static and dynamic mechanical factors have been attributed to decreases in functional residual capacity and decreases in tidal volume in the obese, it is likely that other factors are also involved (Shore and Fredberg, 2005).

A neural network sensitive to leptin and other energy status signals stretching from the hypothalamus to the caudal medulla has been identified as the homeostatic control system for the regulation of food intake and energy balance, i.e. leptin signaling regulates satiety and therefore obesity (Berthoud, 2006, 2007). In the obese, the serum concentration of leptin is elevated (Klok et al., 2007), while in overweight children, current asthmatics have twice the serum level of leptin compared with overweight children without current asthma (Mai et al., 2004). A mechanistic link between obesity/leptin and bronchoconstriction has not been postulated.

4. Pathogenic indicators of asthma: bronchial tone and airway remodeling

The risk factors stress, obesity and menopause act on three interrelated pathways, the serotonergic, leptinergic and reproductive axis. In order to understand how these different systems may interact to induce asthma, I will first describe how each of these systems regulates the two major pathogenic pathways involved in non-allergic adult-onset asthma: (1) bronchial tone, and (2) airway remodeling.

4.1. Regulation of bronchial tone

Contraction of tracheal smooth muscle requires the binding of Ca^{2+} to calmodulin, which then binds to and activates myosin light chain kinase (MLCK). The Ca^{2+}–calmodulin–MLCK complex catalyzes the phosphorylation of myosin, which induces contraction by stimulating the actin-activated Ca^{2+}-ATPase activity of myosin. Relaxation of tracheal smooth muscle is mediated by an increase in cAMP that stimulates a cAMP-dependent protein kinase to catalyze protein phosphorylation that leads to relaxation by decreasing intracellular [Ca^{2+}].

4.1.1. HPG hormones and bronchoconstriction

Few studies have examined the effects of sex hormones on bronchomotor tone. Estrogen receptors (ERα and ERβ) are present on, and estrogen is active, both in vascular smooth muscle and endothelium. Estrogen administration promotes vasodilation both in human and experimental animals, in part by stimulating prostacyclin and nitric oxide synthesis (Farhat et al., 1996). Both prostaglandin synthase and the constitutive nitric oxide synthase are induced by estrogen. Estrogens also induce the production of cAMP (Dubey et al., 2000). In myometrial cells, PGE_1, and PGE_2 but not $PGF_{2\alpha}$ have been found to elevate cAMP (Dubey et al., 2000; Harbon and Clauser, 1971).

No studies have examined the role of other HPG hormones (GnRH, LH/FSH, activins, inhibins) in regulating bronchomotor tone, despite their presence in the lung and the fact that GnRH and LH/FSH receptors are G protein-coupled receptors that also signal via cAMP (Tieva et al., 2001; Abdallah et al., 2004). Decreased secretion of GnRH and LH would be predicted to modulate G protein-coupled receptor (GPCR) signaling leading to decreased cAMP production and muscle contraction. Likewise, decreased secretion of serum estrogen also would be expected to decrease cAMP production and induce muscle contraction.

4.1.2. Serotonin and bronchoconstriction

5-HT and 5-HT agonists, like histamine and methacholine, are well documented bronchoconstrictors (Spector, 1996; Watts and Cohen, 1992). Inhaled 5-HT induces bronchoconstriction in asthmatics but does not produce bronchoconstriction in normal subjects (Cushley et al., 1986). 5-HT exhibits a broad diversity of effects on airway smooth muscle contraction, via a variety of 5-HT receptor subtypes in both airway smooth muscle and efferent nerves (Dupont et al., 1999). In several animal studies, 5-HT has been shown to act directly on airway smooth muscle, causing contraction at low doses and relaxation at high doses. Both contraction and relaxation are mediated by stimulation of

the 5-HT2A receptor on airway smooth muscle (Watts and Cohen, 1992). The mechanism by which 5-HT mediates contraction is unclear, but it has known affects on prostaglandin/cAMP and cholinergic regulation of tone (Rizzo et al., 1993; Takahashi et al., 1995). In this connection, a new anti-asthma drug (4-benzhydryloxy-1-[3-(1H-tetrazol-5-yl)-propyl]piperidine; HQL-79) (Matsushita et al., 1998) strongly inhibits 5-HT (and histamine) induced bronchoconstriction in guinea pigs via the increased release of PGE_2 and decreased release of PGD2 (HQL-79 decreases PGD synthase expression). Therefore, increases in 5-HT would be expected to reduce prostaglandin and cAMP synthesis and promote muscle contraction.

4.1.3. Leptin and bronchoconstriction

Leptin receptors (OBR) are expressed in SMCs (Zeidan and Karmazyn, 2006; Bohlen et al., 2007). Leptin signaling induces the expression of PGF2α and cAMP-specific PDE (Zerani et al., 2004, 2005) while chronic central leptin infusion increases PI3K and PDE3β activities and decreases cAMP levels (Sahu and Metlakunta, 2005). Therefore, chronically increased leptin levels with obesity would be expected to decrease cellular cAMP levels and promote bronchial contraction.

4.2. Airway remodeling

Chronic persistent asthma is characterized by poorly reversible airway obstruction. Histopathological studies of airways removed postmortem from patients with severe asthma reveals marked inflammatory and architectural changes associated with airway wall thickening. Increased airway smooth muscle content, occurring as a result of hyperplastic and/or hypertrophic growth, is believed to be one of the principal contributors to airway wall thickening, inflammation and to reduced airway responsiveness in asthmatics (Hirst, 1996).

4.2.1. HPG hormones and airway remodeling

GnRH has been shown to be proliferative towards a number of different cell lines (e.g. Wauters et al., 1995; Maudsley et al., 2004) including SMCs (Chegini et al., 1996), while a potent GnRH receptor signaling antagonist prevents cell proliferation by inducing TGFβ production (Chegini et al., 2002). Estradiol has been shown to inhibit arterial SMC proliferation (Vargas et al., 1993). Suppression of serum sex steroids would therefore be expected to allow cell proliferation (Bowen and Atwood, 2004).

4.2.2. Serotonin and airway remodeling

5HT promotes, and 5HT antagonists inhibit cell proliferation in a variety of tumor cells (e.g. prostate carcinoma, lung carcinoma and colonic carcinoma; Siddiqui et al., 2005). In the only study performed on rat airway SMC growth, the rate of proliferation of cells exposed to hypoxic conditions was increased (17%) by 5-HT (Cogo et al., 2003). Thus, asthma-induced hypoxia and 5-HT may interact to regulate SMC proliferation.

4.2.3. Leptin and airway remodeling

Leptin induces a time- and dose-dependent increase in human cardiomyocyte proliferation via extracellular signal-regulated kinase- and phosphatidylinositol 3-kinase-dependent signaling pathways (Tajmir et al., 2004). However, while leptin also induces endothelial cell proliferation, angiogenesis and the expression of matrix metalloproteinases (MMP-2, MMP-9, TIMP-1, and TIMP-2), it did not induce cell proliferation of human coronary artery SMCs *in vitro* despite also upregulating MMP-2, MMP-9, TIMP-1 expression (Bouloumie et al., 1998; Park et al., 2001).

5. Interplay between endocrine systems and the development of adult-onset asthma: the 'multi-hit endocrine model of adult-onset asthma'

The above data and observations indicate that in addition to the HPA axis, that the HPG, serotonergic and leptinergic pathways play a pivotal role in regulating bronchial tone. We propose the following model of adult-onset asthma (Fig. 2). Normally, corticosteroids produced naturally or given either as derivatives of cortisone or cortisol, induce the expression of PGE_2 which drives cAMP production and muscle relaxation. However, stress, obesity, depression, and menopause/andropause alter the concentration of cAMP in SMCs as described in the previous section. This model therefore suggests that the level of cellular cAMP, as determined by the *overall* signaling via the

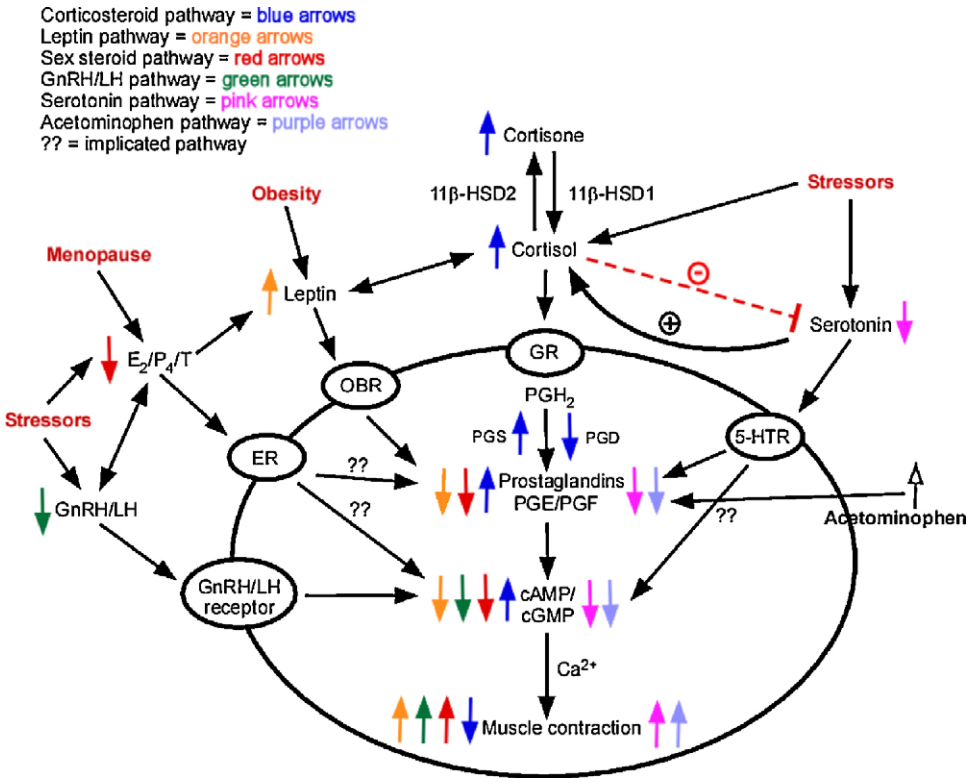

Fig. 2. Signaling via GPCR pathways impact cAMP production and bronchial tone. Normal cAMP levels maintain bronchial tone. However, stressors, obesity and menopause that lead to an overall decrease in cellular cAMP promote bronchial SMC contraction. Chronic supplemental cortisone treatment is the current therapy for increasing cAMP and relaxing the bronchial musculature. E_2 = 17β-estradiol; P_4 = progesterone, T = testosterone.

corticosteroid, HPG, leptinergic and serotonergic pathways, will dictate bronchial tone (Fig. 2). When the inhibition of SMC cAMP synthesis reaches a certain threshold, bronchial tone will change. This threshold could be breached by a combination of life situations. For example, aging increases 5-HT, and age-related changes in sex hormones increase obesity and leptin production. Aging also increases GnRH/LH signaling, but decreases sex steroid signaling. Stress inhibits both GnRH/LH and sex steroid production. The degree of reproductive senescence, depression, obesity and perceived stress will therefore largely dictate bronchial tone and the onset of adult asthma. Circadian changes in the serum concentrations of sex hormones, serotonin, leptin and cortisol, would also impact the duration and timing of bronchoconstriction.

Taking stress as an example, while stress induces cortisol production, it also induces many other hits, including a potential decrease in cellular 5-HT production, a decrease in the production of HPG (GnRH/LH/sex steroids) hormones (Bowen and Atwood, 2004) and an increase in leptin. Cortisol increases serum leptin concentration *in vitro* (Wabitsch et al., 1996) and *in vivo* (Tuominen et al., 1997; Schafroth et al., 2000). Each of these pathways operates through receptors to modulate cAMP and Ca^{2+} metabolism. Therefore, while increasing cortisol would increase cellular cAMP and maintain bronchial tone, it would also increase leptin, and decrease serotonin, gonadotropin and sex steroid levels thereby decreasing cAMP levels. While the contribution of each hormonal system to overall cAMP is unknown, cortisol administration by asthmatics required to prevent bronchoconstriction indicates that these other pathways overwhelm cortisol-induced cAMP generation.

This model is strongly supported by a recent study in pigs examining vasospastic angina (Hizume et al., 2006). This study demonstrated that intracoronary 5-HT causes coronary hyperconstriction and reduces coronary blood flow associated with ischemic ECG changes (coronary vasospasm) in cortisol-treated animals. All of these responses were abolished by hydroxyfasudil, a specific Rho-kinase inhibitor, *in vivo*. Likewise, organ chamber experiments demonstrate that serotonin concentration-dependently caused hypercontractions of coronary vascular smooth muscle associated with Rho-kinase activation (as evidenced by the enhanced phosphorylation of myosin binding subunit, a

substrate of Rho-kinase) in cortisol treated group. All of these responses were again inhibited by hydroxyfasudil *in vitro*. These results indicate that sustained elevation of serum cortisol level sensitizes coronary vasoconstricting responses through Rho-kinase activation, suggesting a link between stress and coronary vasospasm. The model also is supported by the observation that inhaled 5-HT causes bronchoconstriction in asthmatics but not in normal subjects (Cushley et al., 1986).

Another line of evidence that supports the prostaglandin/cAMP pathway in playing a role in bronchoconstriction is seen from studies demonstrating that acetaminophen (Tylenol) inhibits PGE_2 and PGF2α secretion from cultured kidney inner medulla. The decrease in prostaglandins was associated with a corresponding decrease in cyclic AMP content (Zenser et al., 1978). Although not studied, acetaminophen, which has been demonstrated to also modulate calcium metabolism (Salas and Corcoran, 1997), may modulate SMC contraction. This is supported by an increasing body of epidemiological studies indicating that acetaminophen may promote asthma in certain individuals (e.g. Karimi et al., 2006; Baldassarre et al., 2006; McKeever et al., 2005; Eneli et al., 2005; Barr et al., 2004b; Shaheen et al., 2000).

Polymorphisms in genes that regulate prostaglandin/cAMP production via the pathways described in Fig. 2, or that impact prostaglandin or cAMP synthesis or degradation may predispose individuals to asthma. All genetic polymorphisms implicated in asthma from meta-analyses (TNFA, 2-adrenergic receptor, a disintegrin and metalloprotease 33 (ADAM33), CD14, and leukotriene C4 synthase (Contopoulos-Ioannidis et al., 2007) regulate, or are regulated by, cAMP (e.g. Renauld, 2001). Finally, individuals who have or have had adult-onset asthma tend to be far more sensitive to allergens and susceptible to allergic asthma. This suggests an interplay between the endocrine model of intrinsic adult-onset asthma and extrinsic allergic asthma, whereby the background of low SMC cAMP levels in adult-onset asthma makes individuals more sensitive to extrinsic allergens and the triggering of an asthma attack. Indeed, extrinsic allergens may trigger late-onset asthma by further lowering SMC cAMP levels, a mechanism that might also explain early-onset asthma.

6. Therapies based on the multi-hit endocrine model

Corticosteroids are the primary therapy for the treatment of asthma. In adult-onset asthma, high concentrations of cortisol are required to maintain muscle relaxation. As cortisol signaling declines between treatments, so too does the cortisol-induced suppression of serotonin production (Pretorius, 2004), and coupled with the suppressed estradiol/testosterone (and GnRH/LH) signaling and elevated leptin signaling, cAMP levels decrease resulting in muscle contraction.

Potential therapies based on the Multi-Hit Endocrine Model of Intrinsic Adult-onset Asthma would include:

(1) SSRI's. The SSRI citalopram reduces depressive symptoms and improves asthma. 5-HT and SSRIs like citalopram acutely increase serum cortisol in humans (Mashchak et al., 1983; Schule, 2007). Citalopram also may increase glucocorticoid negative feedback on the HPA axis (Pariante et al., 2004), via enhancement of glucocorticoid receptor function through the modulation of membrane steroid transporters (Pariante et al., 2001; Pariante and Miller, 2001) and changes in glucocorticoid receptor binding sites (Hery et al., 2000). Thus, citalopram could potentially have a direct effect at the receptor level on prescription corticosteroid requirements in asthma patients, promoting SMC relaxation and tracheal dilation.
(2) 5-HT receptor antagonists. Beneficial effects of ketanserin, a 5-HT2 antagonist, have been noted on forced 1 second expiratory volume in patients with chronic airflow limitation (Stott et al., 1988).
(3) Prostaglandin synthesis inhibitors. Stress-induced elevations in brain and hypothalamic 5-HT (and cortisol) are attenuated by PG synthesis inhibitors (e.g. declofenac; Bhattcharyya and Sur, 1999). Likewise, the anti-stress effects of Panax ginseng and diazepam may be mediated through prostaglandin modulation of 5-HT (Bhattcharyya and Sur, 1999).
(4) 17β-Estradiol/progesterone/testosterone (Kos-Kudla et al., 2000).
(5) Calcium antagonists such as hydroxyfasudil (Hizume et al., 2006).
(6) Treating obesity.
(7) Combinations of these drugs/strategies.

In addition to relieving bronchoconstriction, corticosteroids and sex steroids, both being differentiative in nature, prevent airway SMC proliferation (Vargas et al., 1993; Stewart et al., 1995). The exact mechanism by which estrogen

treatment reduces collagen synthesis is unknown, although it appears to be related to estrogen's ability to increase cellular cAMP levels (Dubey et al., 2000). 5-HT receptor antagonists (sarpogrelate) and some agonists also prevent SMC proliferation (Saini et al., 2003, 2004). GnRH agonists prevent cell proliferation (Chegini et al., 2002).

7. Conclusions

The Multi-Hit Endocrine Model of Intrinsic Adult-onset Asthma can explain the discrepant epidemiological data associating stress, obesity, depression and menopause with adult-onset asthma and is supported by the basic (Hizume et al., 2006) and clinical (Kos-Kudla et al., 2000; Pariante et al., 2004) data discussed above. As illustrated in Fig. 2, many hormonal pathways related to aging (obesity, menopause/andropause, depression) can downregulate cAMP production, including changes in GPCR signaling by GnRH, LH and 5-HTR, and changes in GR and OBR. An overall decline in cellular cAMP as a result of this signaling would promote bronchoconstriction. Future therapeutics for adult-onset asthma should target modulation of cAMP and prostaglandin synthesis for modulation of SMC contraction and tracheal dilation.

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My father, as a source of hope, inspiration and guidance in dealing with life situations beyond our control.

Conflict of interest

None.

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