long-term and/or high-dose ICS use in young children may negatively affect BMD. The follow-up period in this study was longer than in other studies, but limitations include recall bias and failure to account for other lifestyle factors that may affect BMD. Also, the use of steroid-equivalents as the index of cumulative steroid use limits the generalizability of this study. Because the clinical implications of the decreased BMD are unclear, additional long-term studies are needed. However, this study underscores the importance of judicious use of ICS in young children.

Impact of Asthma Medication and Familial Factors on the Association Between Childhood Asthma and Attention-Deficit/Hyperactivity Disorder: A Combined Twin- and Register-Based Study


PURPOSE OF THE STUDY. Previous research has supported an association between asthma and attention-deficit/hyperactivity disorder (ADHD). The goals of this study were to assess (1) whether asthma is associated with inattentive or hyperactive/impulsive symptoms of ADHD, (2) the impact of asthma severity and asthma medications on ADHD, and (3) the contributions of shared genetic and environmental risk factors on the asthma-ADHD relationship.

STUDY POPULATION. Data were obtained from the Child and Adolescent Twin Study in Sweden (CATSS) and 3 Swedish national registers, which contained information on maternal and child diagnoses and prescribed drug dispensation. The population used in this study included all children born between 1992 and 2002 whose parents were interviewed between August 2003 and August 2011.

METHODS. Diagnoses and severity of asthma were based on responses to questions derived from the International Study of Asthma and Allergies in Childhood and codes from the National Patient Register. Similarly, data about ADHD was retrieved from parental reports, responses to the ADHD and other Comorbidities Inventory and National Patient Register codes. Statistical analyses adjusted for the child’s gender, age, birth weight, gestational age, and maternal socioeconomic variables. The classic twin design was used to assess the relative impact of genetic and environmental factors, both shared and nonshared.

RESULTS. The final study population of 20,072 was restricted to twins with complete answers to the main questions on asthma and ADHD. The overall incidences of asthma and ADHD were 14.0% and ~2%, respectively. Asthma was associated with a nearly twofold increased risk of ADHD, of both subtypes, a link that increased with asthma severity. The overlap of genetic factors was weak. Asthma medications did not affect the risk factors.

CONCLUSIONS. Children with asthma had an increased risk of ADHD, the magnitude of which increased with asthma severity.

Calcium-Sensing Receptor Antagonists Abrogate Airway Hyperresponsiveness and Inflammation in Allergic Asthma


PURPOSE OF THE STUDY. The symptoms of asthma are potentially controllable in most asthmatic patients using conventional therapy, but there is an unmet need for identification of novel asthma therapies that target the root cause of the disease rather than its clinical sequelae.

STUDY POPULATION. Primary human airway smooth muscle (ASM) cells were obtained from surgical lung specimens of patients undergoing lobectomy for focal noninfectious disease, including 5 each from patients with moderate asthma and patients without asthma. For animal studies, mice with calcium-sensing receptor (CaSR) targeted gene ablation within ASM cells were compared with wild-type mice without the gene ablation.

METHODS. CaSR receptor expression, calcium flux, and cell signaling pathways were assessed using molecular methods. Force measurements were conducted in intra-acinar bronchi using a wire myograph, and gene and protein expression of human and murine lung specimens were measured using laser capture microdissection, qRT-PCR and immunofluorescent staining. A mouse model was used to assess effects on airway resistance, inflammation, and allergen-induced responses. The CaSR antagonists NPS89636 and NPS2143 were obtained from NPS Pharmaceuticals and Tocris.
RESULTS. In human bronchial biopsies and in mouse interlobular bronchi, CaSR expression was increased in asthma. In addition, eosinophil polycations such as eosinophil cationic protein and major basic protein activated the human CaSR. Inhibitors of this receptor (“calcilytics”) prevented increases in Ca$^{2+}$ in ASM from patients with asthma. In the mouse model, the mice lacking CaSR did not have polycation-induced bronchoconstriction compared with WT mice. Calcilytics also reduced allergen-induced airway hyperresponsiveness and inflammation in sensitized mice. Finally, calcilytics reduced airway resistance in the murine model of asthma in mice that were sensitized to allergens.

CONCLUSIONS. These data show that a functional CaSR is upregulated in asthmatic ASM and targeted by locally produced polycations to induce hyperresponsiveness and inflammation. Thus, calcilytics may represent effective asthma therapeutics.

REVIEWER COMMENTS. The authors show that elevated extracellular calcium can activate airway smooth muscle cells through the calcium-sensing receptor (CaSR) and that these receptors are increased in asthma. In addition, CaSR antagonists can prevent bronchoconstriction in response to eosinophil granular proteins and thus show great promise for development as a novel treatment of asthma.

Effect of a Soy Isoflavone Supplement on Lung Function and Clinical Outcomes in Patients With Poorly Controlled Asthma: A Randomized Clinical Trial


PURPOSE OF THE STUDY. A number of studies have suggested a potential role for dietary factors as modifiers of asthma severity. This study assessed whether a soy isoflavone supplement improves asthma control in patients with poorly controlled asthma.

STUDY POPULATION. Three hundred eighty-six subjects ≥12 years old with symptomatic, poorly controlled asthma were enrolled from 19 adult and pediatric pulmonary and allergy centers in the American Lung Association Asthma Clinical Research Centers network.

METHODS. In this multicenter, randomized, double-blind, placebo-controlled trial, subjects were randomized (1:1) to receive either a soy isoflavone supplement or placebo twice daily for 6 months. The primary outcome measure
Calcium-Sensing Receptor Antagonists Abrogate Airway Hyperresponsiveness and Inflammation in Allergic Asthma

Frederick J. Rubner and James E. Gern

Pediatrics 2015;136;S269

DOI: 10.1542/peds.2015-2776

Updated Information & Services
including high resolution figures, can be found at:
/content/136/Supplement_3/S269.2.full

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
/site/misc/reprints.xhtml
Calcium-Sensing Receptor Antagonists Abrogate Airway Hyperresponsiveness and Inflammation in Allergic Asthma

Frederick J. Rubner and James E. Gern

Pediatrics 2015;136;S269
DOI: 10.1542/peds.2015-2776PPPP

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/136/Supplement_3/S269.2.full