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Abstract

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Grant Number:	5K08HL003343-05
PI Name:	KRAFT, MONICA
PI Email:	kraftm@njc.org
PI Title:	ASSOCIATE PROFESSOR OF PULMONARY SCIENCE
Project Title:	EOSINOPHIL INFLUX INTO THE LUNG IN NOCTURNAL ASTHMA

Abstract: DESCRIPTION (Adapted from the applicant's abstract) Circadian changes in airway function are an important aspect of asthma, as more than 70% of deaths and 80% of respiratory arrests occur during sleep related hours. This alteration in airway function has been linked to eosinophils, which have been shown to be increased at night in the airways of asthmatic patients. However, little is known about the mechanisms of nocturnal worsening of asthma, nocturnal asthma (NA). The global hypothesis of this proposal is that NA is due to production of specific cytokines by activated T lymphocytes in response to a low serum cortisol. These activated T cell products induce a reduction of glucocorticoid receptor (GR) binding affinity and result in increased eosinophil influx into the lung, thus decreasing lung function at night. After initially determining the GR binding affinity of peripheral blood lymphocytes in subjects with NA, non-nocturnal asthma (NNA) and control subjects, the proposal will evaluate if this alteration is inducible in-vitro by the activated T cell products interleukin (IL)-2 and IL-4. These cytokines have been shown to reduce GR binding affinity in steroid resistant asthmatics. If our hypothesis is correct, then T cell IL-2, IL-4, IL-5 and granulocyte-macrophage colony stimulating factor (GMCSF) MRNA expression and product in lung tissue and bronchoalveolar lavage fluid at four time points will be evaluated. IL-5 and GMCSF are involved in eosinophil differentiation and survival, thus their presence is important in evaluation of the kinetics of eosinophil influx into the lung. To determine the effect of decreasing endogenous corticosteroids at night on T lymphocyte function and eosinophil influx, physiologic doses of hydrocortisone to block the nocturnal nadir of cortisol will be infused. To further clarify this relationship, metyrapone will be used to block cortisol output by the adrenal gland. If the hypothesis is correct, hydrocortisone infusion will alter T cell production of the above described cytokines and thereby increasing GR binding affinity. Conversely, metyrapone will result in the opposite effect. The end result will be either an improvement (hydrocortisone infusion) or decrement (metyrapone administration) in lung function. The information gained from this proposal will determine the mechanisms and timing of nocturnal eosinophil influx produced by reduced glucocorticoid receptor binding affinity in the face of low serum cortisol. This information has mechanistic and therapeutic importance for nocturnal asthma, and asthma in general.

Thesaurus Terms:
asthma, cell migration, circadian rhythm, cytokine, eosinophil, sleep
T lymphocyte, colony stimulating factor, corticosteroid receptor, cortisol, hormone regulation /control mechanism, interleukin 2, interleukin 4, interleukin 5, leukocyte activation /transformation, metyrapone, respiratory function
biopsy, clinical research, human subject, tissue /cell culture

Institution:	NATIONAL JEWISH MEDICAL & RES CTR AND RESEARCH CENTER DENVER, CO 80206
Fiscal Year:	2000
Department:	
Project Start:	01-AUG-1996
Project End:	31-JUL-2001
ICD:	NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
IRG:	ZHL1

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Grant Number: 5M01RR000051-391027
PI Name: KRAFT, MONICA
PI Email:
PI Title:
Project Title: EOSINOPHIL INFLUX INTO THE LUNG IN NOCTURNAL ASTHMA

Abstract: The major goal of this protocol is to carefully characterize nocturnal asthma as a model of inflammation and determine the mechanisms of recruitment of the main effector cell, the eosinophil. The overall hypothesis to be tested is that neurohormonal changes, particularly the nocturnal fall in endogenous cortisol, results in increased inflammation in the airways and parenchyma of the lung in subjects with nocturnal asthma.

Thesaurus Terms:
asthma, eosinophil, pulmonary circulation
cortisol, inflammation, neurohormone
clinical research, human subject

Institution: UNIVERSITY OF COLORADO HLTH SCIENCES CTR
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Fiscal Year: 2000
Department:
Project Start:
Project End:
ICD: NATIONAL CENTER FOR RESEARCH RESOURCES
IRG:

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Grant Number:	5M01RR000051-391080
PI Name:	KRAFT, MONICA
PI Email:	
PI Title:	
Project Title:	COMPARISON OF CLINICAL BENEFIT, ANTIINFLAMMATORY EFFECT

Abstract: This study is designed to examine the importance of inflammation and of anti-inflammatory therapy in moderate asthma. Some of the specific aims of this study are: 1) efficacy in reducing symptoms, reducing bronchial reactivity and improving peak flow 2) efficacy in reducing the numbers of inflammatory cells and concentrations of inflammatory mediators recovered from the airways 3) duration of therapeutic benefit after cessation of therapy and 4) systemic toxicity. This study also is designed to examine the safety and efficacy of methacholine challenge in the evaluation of subjects with moderate asthma.

Thesaurus Terms:
asthma, beta adrenergic agent, drug screening /evaluation, human therapy evaluation, inflammation, respiratory disorder chemotherapy, triamcinolone
clinical trial, inhalation drug administration
bronchoscopy, clinical research, diagnostic respiratory lavage, human subject

Institution:	UNIVERSITY OF COLORADO HLTH SCIENCES CTR 4200 E 9TH AVE DENVER, CO 80262
Fiscal Year:	2000
Department:	
Project Start:	
Project End:	
ICD:	NATIONAL CENTER FOR RESEARCH RESOURCES
IRG:	

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Grant Number: 3M01RR000051-39S11027
PI Name: KRAFT, MONICA
PI Email:
PI Title:
Project Title: EOSINOPHIL INFLUX INTO THE LUNG IN NOCTURNAL ASTHMA

Abstract: The major goal of this protocol is to carefully characterize nocturnal asthma as a model of inflammation and determine the mechanisms of recruitment of the main effector cell, the eosinophil. The overall hypothesis to be tested is that neurohormonal changes, particularly the nocturnal fall in endogenous cortisol, results in increased inflammation in the airways and parenchyma of the lung in subjects with nocturnal asthma.

Thesaurus Terms:
asthma, eosinophil, pulmonary circulation
cortisol, inflammation, neurohormone
clinical research, human subject

Institution: UNIVERSITY OF COLORADO HLTH SCIENCES CTR
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Fiscal Year: 2000
Department:
Project Start:
Project End:
ICD: NATIONAL CENTER FOR RESEARCH RESOURCES
IRG:

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Grant Number:	3M01RR000051-39S11080
PI Name:	KRAFT, MONICA
PI Email:	
PI Title:	
Project Title:	COMPARISON OF CLINICAL BENEFIT, ANTIINFLAMMATORY EFFECT

Abstract: This study is designed to examine the importance of inflammation and of anti-inflammatory therapy in moderate asthma. Some of the specific aims of this study are: 1) efficacy in reducing symptoms, reducing bronchial reactivity and improving peak flow 2) efficacy in reducing the numbers of inflammatory cells and concentrations of inflammatory mediators recovered from the airways 3) duration of therapeutic benefit after cessation of therapy and 4) systemic toxicity. This study also is designed to examine the safety and efficacy of methacholine challenge in the evaluation of subjects with moderate asthma.

Thesaurus Terms:
asthma, beta adrenergic agent, drug screening /evaluation, human therapy evaluation, inflammation, respiratory disorder chemotherapy, triamcinolone
clinical trial, inhalation drug administration
bronchoscopy, clinical research, diagnostic respiratory lavage, human subject

Institution:	UNIVERSITY OF COLORADO HLTH SCIENCES CTR 4200 E 9TH AVE DENVER, CO 80262
Fiscal Year:	2000
Department:	
Project Start:	
Project End:	
ICD:	NATIONAL CENTER FOR RESEARCH RESOURCES
IRG:	

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Grant Number:	1R01HL064619-01
PI Name:	KRAFT, MONICA
PI Email:	kraftm@njc.org
PI Title:	ASSOCIATE PROFESSOR OF PULMONARY SCIENCE
Project Title:	NOCTURNAL ASTHMA: LINKING INFLAMMATION AND REMODELING

Abstract: Nocturnal worsening of asthma, hereby referred to as nocturnal asthma, affects up to 75% of chronic stable asthmatics. It is characterized by decreased lung function at night in associated with increased inflammatory cell influx into the airways and alveolar tissue. Because it is a naturally occurring, unchallenged model of asthma in humans, unique mechanistic information about the inflammatory response can be obtained. In this proposal, mechanisms governing the inducing of steroid resistance by increased inflammation at night and how these mechanisms governing the induction of steroid resistance by increased inflammation at night and how this process modulates the airway remodeling process will be determined. The global hypothesis of this proposal is that cytokines, interleukin (IL)-4 and IL-13, are increased at night and induce a state of reduced steroid responsiveness. This state further enhances the production of other inflammatory mediators, such as tumor necrosis factor-alpha) by the alveolar macrophage. This increased inflammation culminates in enhanced necrosis factor-alpha (TNF-alpha) by the alveolar macrophage. This increased inflammation culminates in enhanced airway fibroblast leading to airway structural changes or remodeling. To confirm or refute this hypothesis, the first specific aim will determine if glucocorticoid receptor-beta (GR-beta), a form of the glucocorticoid receptor that is not transcriptionally active, is increased at night in nocturnal asthma, and whether its expression is associated with reduced steroid responsiveness at night in nocturnal asthma, and whether its expression is modulated by the cytokines IL-4 and IL-13. The third and fourth specific aims will determine whether these cytokine salter airway fibroblast function and enhance the remodeling process. Specifically, specific aim 3 will determine whether receptors for GR-beta, IL-4 and IL- 13 are present on the airway fibroblast, and whether these cytokines modulate GR-beta expression in the fibroblast. The fourth specific aim will determine whether IL-4 and IL-13 promote airway remodeling by directly altering fibroblast function, or by inducing a functional state of corticosteroid resistance. We will also determine if the effects of IL-4 and IL-13 on fibroblasts are enhance by production of TNF-alpha, as it is increased at night in nocturnal asthma, and exerts fibrogenic properties. The significance of this proposal is that it will add important information regarding the pathophysiology of airway inflammation and the airway structural changes we refer to as airway remodeling.

Through understanding of the effects of IL-4 and IL-13 on GR-beta regulation in airway inflammatory cells and fibroblasts, and the functional consequences of reduced steroid responsiveness, direct therapeutic strategies can be designed to decreased inflammation, alter the remodeling process and ultimately improve asthmatic symptoms and lung function.

Thesaurus Terms:
asthma, cytokine, fibrogenesis, inflammation, sleep
alveolar macrophage, cell growth regulation, corticosteroid receptor, fibroblast, hormone regulation /control mechanism, interleukin 13, interleukin 4, longitudinal human study, tumor necrosis factor alpha
clinical research, human subject

Institution:	NATIONAL JEWISH MEDICAL & RES CTR AND RESEARCH CENTER DENVER, CO 80206
Fiscal Year:	2000
Department:	
Project Start:	01-APR-2000
Project End:	31-OCT-2005
ICD:	NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
IRG:	LBPA