311P INFLAMMATION AND PAIN IN THE AGEING POPULATION

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The initial rapid mediation of an individual's response to injury is through activation of small diameter myelinated (Aδ) and unmyelinated (C) primary afferent neurons. This so called neurogenic inflammation results in vasodilatation and plasma extravasation, often presumed to be initiated through an axon reflex mechanism, and transmission of modified noxious information to the cerebral cortex to register the multiple dimensions of the pain experience. Both these pathways are altered by the ageing process which probably results in clinically relevant changes in tissue healing and pain sensitivity with age. These phenomena have been sufficiently well examined in complementary animal and human models to allow for some generalised observations to be made on the responsible mechanisms.

Both vasodilatation and plasma extravasation are reduced by ageing. These processes, mediated by neuromodulators such as Substance P, neurokinin A and calcitonin gene-related peptide contained in small diameter afferents with polymodal nociceptors, are mainly reduced as a consequence of reduced synthetic activity within the dorsal root ganglia (DRGs), although a reduction in numbers of nerves cannot be totally disregarded. The sensitivity of polymodal nociceptors themselves may also be reduced with age. Intrinsic compensatory mechanisms including an increase in nitric oxide synthase activity within sensory nerves and supersensitivity of peripheral peptide receptors are known to develop with age. This, together with intact smooth muscle reactivity with advancing age, suggest a potential for reversing impaired healing in older persons, through direct end-organ or nerve stimulation. This effect has thus far only been demonstrated in animal models.

Similarly, pain threshold is increased to noxious chemical, thermal and mechanical stimulation with age. This is attributed to down-regulation of the pain pathway and the slowing of the central cognitive processing of noxious information. Older people also depend more on 'C' fibres when interpreting quality of pain. In addition, central nervous system inhibitory modulation of primary afferent noxious input is impaired with age, perhaps resulting in enhanced secondary hyperalgesia (tenderness) and diminished pain tolerance once pain is induced.

The complex modulation of these processes, here illustrated by the variations produced by age, suggest that neurogenic inflammation and pain are particularly important for living organisms.

312P COPD: THE NEED FOR NEW TREATMENTS

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COPD affects 6% of the population in the UK. Despite comprehensive smoking cessation programmes and changes in attitudes to cigarette smoking, the incidence of this disease continues to rise, particularly in countries outside Europe and North America. At present there are no therapeutic strategies available that can truly alter disease progression. Patients with COPD invariably present to primary care at a stage when disease is well established. Currently, COPD is deemed as a chronic inflammatory disease of the airways in which patients have irreversible airflow obstruction in the presence of cough and mucopurulent sputum.

Until recently, there have been no major randomised controlled trials to assess the possible disease-modifying benefits of anti-inflammatory agents such as inhaled corticosteroids in COPD. Previously, trials of bronchodilators had shown symptomatic improvement without any arrest in decline of lung function when compared to placebo. Indeed, of all of the therapeutic interventions, only smoking cessation resulted in prevention of decline in lung function. Three recent studies on the benefits of inhaled corticosteroids have been presented at International meetings and are in the public domain: EUROSCOP, ISOLDE and the Copenhagen Lung Health study. The data from these trials show conflicting results. Patients in EUROSCOP were persistent smokers, had mild impairment in lung function, entered a placebo controlled parallel group study over three years and only those patients with a lower smoking history appeared to benefit from inhaled corticosteroids. This effect was seen during the first nine months of treatment. The ISOLDE study was similar in design. Patients were smokers or ex-smokers, had more severe disease and showed small but sustained benefits in terms of quality of life and in lung function over 3 years whilst taking inhaled corticosteroids when compared to placebo. The Copenhagen Lung Health study was negative.

More recently, there has been interest in the role of long-acting β-agonists. Salmeterol improves quality of life and lung function in patients with severe disease. Whether or not this is a smooth muscle phenomenon or some other property of salmeterol remains to be evaluated; likewise, eformoterol is undergoing clinical trials in COPD with a view to assessing outcomes such as quality of life, improvement in lung function and exercise tolerance. A new long acting anticholinergic agent, tiotropium bromide, that has kinetic selectivity rapidly dissociating from M2 receptors but slowly from M1 and M3 receptors, has shown promise in early clinical trials. This selective muscarinic antagonist provides sustained bronchodilatation for up to 24 hours.

There is evidence that excess protease activity contributes to COPD pathology. Several antiprotease strategies are underway including the development of neutrophil elastase inhibitors and matrix metalloproteinase inhibitors. Drugs that inhibit mucous hypersecretion including tachykinin antagonists, N-acetyl cysteine, nebulised recombinant human DNAase and even the macrolide antibiotics have been evaluated in COPD without convincing effects.

The most exciting data available is the recent observation that a potent PDE_4 inhibitor (Ariflo™) caused a 10% improvement of lung function after 6 weeks of treatment when compared to placebo in patients with moderate COPD. The mechanism of this remains to be understood. The pathophysiology underlying COPD is unclear but it appears to be a neutrophil-driven disease. It is likely therefore that drugs such as PDE_4 inhibitors may be targeting the neutrophil. However, the benefits of inhaled corticocosteroids in stable disease would appear to be minimal if this were the case, as steroids have no effect on neutrophil function. During exacerbations of COPD, eosinophilic inflammation plays a role and may explain the small benefits seen with inhaled corticosteroids in the studies outlined above.

The challenge for the future is to develop drugs that are specifically targeted at the underlying inflammatory process. On the assumption that the neutrophil is the key driver of disease, treatments that may interfere with neutrophil chemotaxis or neutrophil function may prove successful. For example, modulation of leukotriene B_4 activity by inhibition of synthesis using agents such as 5-lipoxygenase inhibitors or FLAP inhibitors or specific receptor blockade may be beneficial. Drugs targeted against IL8 and TNFα activity may also prove to be of promise. Humanised monoclonal antibodies against TNFα and soluble TNFα receptors have been developed and are in clinical trials for other diseases.

313P REMODELLING OF TISSUES: IMPLICATIONS FOR AGEING AND NOVEL TREATMENT REGIMES

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Acute inflammation is a beneficial, non-specific response of tissues to injury and generally leads to repair and restoration of the normal structure and function In contrast, asthma represents a chronic inflammatory process of the airways followed by healing whose end-result is an altered structure referred to as a remodelling of the airways. Repair usually involves two distinct processes: regeneration, which is the replacement of injured tissue by parenchymal cells of the same type, and replacement by connective tissue and its eventual maturation into scar tissue. In many instances both processes contribute to the healing response and inflammation.

In asthma the processes of cell dedifferentiation, migration, differentiation and maturation, as well as of connective tissue deposition, are frequently associated with altered restitution of airways structure and function. There are several features indicating that asthma is characterised by altered healing and repair processes, such as the presence of myofibroblasts and the increased number of fibroblasts, the hyperplasia of smooth muscle cells and mucous glands, and the altered homeostasis of the extracellular matrix leading to collagen deposition and elastolysis. Most of these features are seen in almost all asthmatics whatever the severity or duration or etiology of asthma, and their reversibility under anti-inflammatory treatments is still not completely known. In this regard, while the increased thickness of the reticular layer of the basement membrane may be reduced by steroids, smooth muscle hypertrophy and mucous gland enlargement appear to be permanent abnormalities.

The end result of all these structural alterations is a tremendous increase of airway wall thickness which, particularly in the more severe forms of the disease, causes a markedly and permanently reduced airways caliber. These features result in an increased resistance to airflow, particularly when there is bronchial contraction and bronchial hyperresponsiveness. The effect on airflow is compounded by the presence of increased mucous secretion and inflammatory exudate, which not only blocks the airway passages but causes an increased surface tension favouring airway closure.

Although the clinical consequences of airway remodelling are not fully understood, it is conceivable that this process can directly contribute to lung senescence as well as to the progressive lung function loss over the years.

314P ENDOTHELIUM-DERIVED NITRIC OXIDE

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The finding that the biological actions of endothelium-derived relaxing factor are due to the endogenous release of nitric oxide (NO) revealed the existence of a ubiquitous biochemical pathway. Nitric oxide is formed from the amino acid L-arginine by a family of enzymes, the NO synthases (NOS), of which several isoforms are now known to exist. The constitutive NOS that was first discovered in the vascular endothelium has been designated as eNOS, whereas that present in the brain, spinal cord and peripheral nervous system is termed nNOS. A third form, induced by immunological or inflammatory stimuli, is known as iNOS.

The discovery of the L-arginine:NO pathway has led to many new insights into cardiovascular physiology and pathophysiology. The synthesis of NO by the vascular endothelium is a vasodilator mechanism which plays a role in the physiological regulation of blood flow and pressure in animals and man. Inhibition of its generation by arginine analogues such as NG-monomethyl-L-arginine (L-NMMA) leads to marked regional vasoconstriction and a hypertensive response. Mice in which the eNOS gene has been disrupted and which specifically lack eNOS have an elevated blood pressure compared with their wildtype counterparts. Nitric oxide also contributes to the control of platelet aggregation and the regulation of cardiac contractility. These physiological effects of NO are all mediated by the action of a constitutive NO synthase and subsequent activation by NO of the soluble guanylate cyclase. Other actions of endothelium-derived NO include attenuation of white cell adhesiveness and inhibition of smooth muscle cell proliferation. Impaired production of NO by eNOS has been implicated in several cardiovascular disorders, including hypertension, vasospasm and atherosclerosis.

Immunological stimuli such as endotoxin lipopolysaccharide and cytokines induce iNOS in many cells and tissues. This enzyme, which was originally identified in macrophages, contributes to the cytotoxic actions of these cells. The NO produced by this enzyme in the cardiovascular system contributes to the profound vasodilatation of septic shock, the hyperdynamic state of cirrhosis and to some inflammatory conditions of the heart. L-NMMA, when used at low doses in animals and man, reverses the hypotension and the hypereactivity to vasoconstrictors characteristic of shock. Selective inhibitors of iNOS will undoubtedly prove beneficial for the treatment of the hypotension of shock or cytokine therapy as well as dilated cardiomyopathy, cirrhosis and other vascular conditions in which this enzyme is induced.

Thus NO generated by endothelial cells can act both as a physiological mediator and as a pathophysiological entity. One way in which this dual action may be achieved is through the actions of NO on mitochondrial function. At low physiological concentrations NO inhibits cytochrome c oxidase in a reversible manner which is competitive with oxygen; this would allow cells to adapt to acute changes in their environment. At higher concentrations NO irreversibly inhibits other enzymes in the respiratory chain, either directly or via the formation of peroxynitrite. This inhibition contributes to the pathological actions of NO.