Oxidative Stress, Nuclear Factor-κB Pathway and Current Smoking in Graves’ Ophthalmopathy

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Dear Sir,

Increased generation of reactive oxygen species (ROS) is thought to play a role in the pathogenesis of Graves’ ophthalmopathy (GO) [1, 2]. Selenium (Se) is an antioxidant agent that has been recently shown to improve significantly the course of mild GO [2]. There is good evidence that oxidative stress plays a role in GO: orbital fibroblasts of GO patients have higher contents of malondialdehyde, superoxide anions and hydrogen peroxide than control orbital fibroblasts [3]. Orbital fibroblasts are recognized as the prime target cells of the autoimmune attack in GO [3].

We suggest a possible interplay between nuclear factor-κB (NF-κB), pro-inflammatory cytokines (which activate and are activated by NF-κB, by amplifying and perpetuating orbital inflammation), ROS, Se and glucocorticoids (GC) (fig. 1) in GO [4, 5]. Many of the GC effects are mediated through an inhibition of NF-κB [6] (fig. 1). GC binding to its receptor may have a dual effect on gene activation such as activation of transcription (transactivation) or a suppression of transcription (transrepression) by interacting with NF-κB; consequently, the production of anti-inflammatory proteins is increased (transactivation), whereas the inflammatory ones are diminished (transrepression) [7].

In our view, the decreased efficacy of GC therapy in current smokers [8] might be explained – at least in part – by the antagonism GC – ROS revealed at the NF-κB level [4] (fig. 1). Cigarette smoking is a major source of ROS.

Future studies (immunosuppressive therapy plus Se) in patients with more severe GO are, at least in part, justified by the following data: (a) GC [6, 7] and Se [9] seem to have a similar inhibitory (possibly synergistic) effect on NF-κB activity (fig. 1), and (b) opposite effects on the NF-κB pathway of current smoking (stimulatory effect via a prooxidant effect) [5] and Se (inhibitory effect via an antioxidant action) [9] (fig. 1). Therefore, a detailed analysis of the influence of smoking upon any antioxidant therapy in patients with GO would be valuable.

Disclosure Statement

The authors have no conflicts of interest to disclose.

Fig. 1. Positive regulatory loop of pro-inflammatory cytokines (IL-1 = interleukin-1, TNF-α = tumor necrosis factor-α) and NF-κB regulated by GC, Se and ROS in GO. Cigarette smoking is a major source of ROS.
References


Erratum

In the article ‘Side Effects of Anti-Thyroid Drugs and Their Impact on the Choice of Treatment for Thyrotoxicosis in Pregnancy’ by Taylor and Vaidya [Eur Thyroid J 2012;1:176–185], the sentence in the right column on line 1, p. 179: ‘Furthermore, there has been a reported case of aplasia cutis secondary to PTU exposure during pregnancy and choanal atresia [37].’ should correctly read: ‘Furthermore, there has been a reported case of choanal atresia secondary to PTU exposure during pregnancy [37].’