Rosiglitazone Cools Down Inflammation in the Metabolic Syndrome

Katherine Esposito, Miryam Ciotola, Domenico Merante, Dario Giugliano

To the Editor:

We read with interest the article by Samaha et al.1 demonstrating a favorable effect of short-term rosiglitazone treatment on the inflammatory milieu in nondiabetic subjects with low high-density lipoprotein cholesterol and the metabolic syndrome. Almost simultaneously, the same group reported similar effects of pioglitazone in subjects with the metabolic syndrome.2 The proinflammatory state that accompanies the metabolic syndrome is associated with both insulin resistance and endothelial dysfunction, providing a connection between inflammation and metabolic processes which is highly deleterious for vascular function.3 PPAR-γ agonists have displayed unique characteristics, in both animal and clinical studies, indicating that they have antiatherogenic properties.4 These compounds may have direct beneficial effects on cardiovascular risk independent of their hypoglycemic action.5 Two pilot studies with troglitazone6 and pioglitazone7 have shown reduced carotid intima-media thickness in patients with type 2 diabetes mellitus. Moreover, a placebo-controlled study showed reduced progression of the intima-media thickness of the common carotid artery in nondiabetic patients who were treated with rosiglitazone.8

More recently, pioglitazone reduced the composite of all-cause mortality, non-fatal myocardial infarction, and stroke in patients with type 2 diabetes mellitus. Moreover, a placebo-controlled study showed reduced progression of the intima-media thickness of the common carotid artery in nondiabetic patients who were treated with rosiglitazone.8

Nuclear factor κB (NF-κB) plays a central role in inflammation and atherogenesis. NF-κB is normally bound to IκB in the cytosol which prevents its movement into the nucleus. Phosphorylation of IκB (α and β) promotes its ubiquitination and subsequent degradation by the proteasome, releasing NF-κB to translocate into the nucleus where it induces the transcription of proinflammatory cytokines.10 As rosiglitazone may inhibit ubiquitin–proteasome activity,11 it is possible that part of its antiinflammatory effect may be mediated by interference with the ubiquitin–proteasome system, but this has never been tested in the metabolic syndrome.

We evaluated the effect of rosiglitazone in cultures of blood monocytes taken from subjects with the metabolic syndrome. Subjects had to have three or more of the following criteria to meet the diagnosis of the metabolic syndrome, as recommended by the Adult Treatment Panel III.12 Subjects were excluded if they had diabetes mellitus, cardiovascular disease, or if they took any medication. Peripheral monocytes were purified and cultured as described by Fitzsimmons et al.13 In brief, human monocytes were isolated from whole blood and identified by flow cytometry analysis according to their characteristic forward and side scatter on a Becton Dickinson FACScan flow cytometer. Monocytes from subjects with the metabolic syndrome (24 × 10^6/mL of DME) were cultured in the presence or absence of pretreatment (48 hours) with rosiglitazone (70 μmol/L). At the end of the incubation adherent monocytes were scraped, collected, lysed, and ubiquitin, proteasome 20S, and NF-κB were evaluated. Ubiquitin and IκB-β were quantified using a specific ELISA Kits (Santa Cruz; R&D Systems; Imgenex).

For the quantitative measurement of the proteasome 20S activity a specific SDS-activation kit (Boston Biochem) was used; the activated form of the NF-κB subunit p65 was assessed with Cellular Activation of Signaling ELISA (CAS) Kit for NF-κB p65.

The 10 subjects (5 men and 5 women) with the metabolic syndrome had a mean age of 42 ± 3.2 years (mean ± SD) and a body mass index of 28.3 ± 3.1 kg/m². Compared with 10 subjects without the metabolic syndrome matched for age, sex, and BMI, subjects with the metabolic syndrome showed higher monocyte content of ubiquitin, proteasome 20S, and NK-κB p65 activity, and lower IκB-β levels (data not shown). The effect of rosiglitazone added to cultures of monocytes is shown in the Figure. Monocyte levels of ubiquitin, activated NF-κB p65, and proteasome 20S were significantly lower after rosiglitazone, whereas IκB-β levels were significantly higher after treatment.

This study demonstrates enhanced ubiquitin–proteasome activity in monocytes from subjects with the metabolic syndrome, associated with NF-κB–dependent increase in inflammatory potential. By reducing ubiquitin–proteasome activity, rosiglitazone interferes with the degradation of IκB-β allowing NF-κB to remain in the cytosol, thus smoothing the transcription of proinflammatory cytokines.
The novel findings of the present study suggest an additional effect of rosiglitazone in reducing the inflammatory burden in subjects with the metabolic syndrome.

References
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