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Abstract:

S-nitrosoglutathione reductase (GSNOR) also known as glutathione- dependent formaldehyde dehydrogenase (FDH), is a zinc-dependent dehydrogenase. GSNOR oxidizes long chain alcohols to an aldehyde with the help of a molecule of NAD+. GSNOR was initially identified as FDH because of its role in the formaldehyde detoxification pathway. The only S-nitrosothiol (SNO) substrate recognized by GSNOR is GSNO. A transnitrosation reaction transfers NO from nitrosylated proteins or S-nitrosothiols (RSNO) to glutathione to form S-nitrosoglutathione. This GSNO is finally converted to glutathione disulfide (GSSG) by a two step mechanism. Cellular GSNO is a nitric oxide reservoir that can either transfer to or remove from the proteins a NO group. Reduction of GSNO by GSNOR depletes this reservoir and therefore indirectly regulates protein nitrosylation. GSNOR inhibitors which can increase the basal GSNO levels will be another potential therapy. Several GSNOR inhibitors were identified in our laboratory and the aim of this study was to understand their cellular effects. One of the experiments studied the effect of the compound on protein-SNO. The role of nitric oxide in regulation of NF-κB pathway is reviewed by Bove and van der Vliet. We focused on identification of nitrosylated proteins

using protein specific antibodies. We identified nitrosylation of IKKβ. So the question raised was whether nitrosylation of IKKβ affects its activity. IKKβ is responsible for phosphorylation of IκBα and phosphorylation of IκBα results in its degradation and activation of NF-κB pathway. Therefore, we studied the phosphorylation of IκBα in the presence of inhibitor C3. Results showed a dose-dependent decrease of pIκB. So the next question was whether the phosphorylation of IKKβ was affected by nitrosylation. We did not detect any change in pIKKβ with different concentrations of C3. The decreased degradation of IκBα caused by C3 translated into decreased NF-κB activity as seen by a dose-dependent decrease in amounts of ICAM-1 with increasing C3 concentration. This data supports the premise that the activity of transcription factor NF-κB is suppressed by inhibiting GSNOR with compound C3

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