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Canthin-6-One Alkaloid Inhibits NF-κB and AP-1 Activity: An Inhibitory Action At Transcriptional Level

Authors : Fadia Gafri, Kathryn Mckintosh, Louise Young, Alan Harvey, Simon Mackay, Andrew Paul, Robin Plevin

Abstract : Nuclear factor-kappa B (NF-κB) is a ubiquitous transcription factor found originally to play a key role in regulating inflammation. However considerable evidence links this pathway to the suppression of apoptosis, cellular transformation, proliferation and invasion (Aggarwal et al., 2006). Moreover, recent studies have also linked inflammation to cancer progression making NF-κB overall a promising therapeutic target for drug discovery (Dobrovolskaia & Kozlov, 2005). In this study we examined the effect of the natural product canthin-6-one (SU182) as part of a CRUK small molecule drug discovery programme for effects upon the NF-κB pathway. Initial studies demonstrated that SU182 was found to have good potency against the inhibitory kappa B kinases (IKKs) at 30μM in vitro. However, at concentrations up to 30μM, SU182 had no effect upon TNFα stimulated loss in cellular IκBα or p65 phosphorylation in the keratinocyte cell line NCTC2544. Nevertheless, 30μM SU182 reduced TNF-α / PMA-induced NF-κB-linked luciferase reporter activity to (22.9 ± 5%) and (34.6± 3 %, $P<0.001$) respectively, suggesting an action downstream of IKK signalling. Indeed, SU182 neither decreased NF-κB-DNA binding as assayed by EMSA nor prevented the translocation of p65 (NF-κB) to the nucleus assessed by immunofluorescence and subcellular fractionation. In addition to the inhibition of transcriptional activity of TNFα-induced NF-κB reporter activity SU182 significantly reduced PMA-induced AP-1-linked luciferase reporter activity to about (48± 9% at 30μM, $P<0.001$) . This mode of inhibition was not sufficient to prevent the activation of NF-κB dependent induction of other proteins such as COX-2 and iNOS, or activated MAP kinases (p38, JNK and ERK1/2) in LPS stimulated RAW 264.7 macrophages. Taken together these data indicate the potential for SU182 to interfere with the transcription factors NF-κB and AP-1 at transcriptional level. However, no potential anti-inflammatory effect was indicated, further investigation for other NF-κB dependent proteins linked to survival are also required to identify the exact mechanism of action.

Keywords : Canthin-6-one, NF-κB, AP-1, phosphorylation, Nuclear translocation, DNA-binding activity, inflammatory proteins.
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