Characterization and environmental influences on inflammatory and physiological responses

av

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ABSTRACT

Pharmaceuticals are regularly released into the environment, in particular non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics. The measured concentrations are relatively low and have therefore been considered to be harmless. However, several pharmaceuticals, including naproxen and atenolol, are stable for up to 1 year in the environment, which increases the risk for accumulation. Evaluation of the effects of pharmaceuticals on induced inflammatory responses is therefore necessary for the assessment of potential risks. Since NF-κB and MAPK are the main pathways known to be critical regulators of inflammatory responses, intracellular signalling and effects on these systems were examined in vitro using human cell-lines. NSAIDs were shown to significantly reduce NF-κB activity at environmentally relevant concentrations. Suppression of immune responses may lead to progressive infections since inflammatory responses are controlled by a cooperative activity of AP-1 and NF-κB. Alterations in the activity of transcription factors and pro-inflammatory cytokine and chemokine levels such as TNF, IL-6 and CXCL8 are associated with several human diseases including cystic fibrosis and AIDS. PMA exposure resulted in a rapid NF-κB activation, while extended treatment suppressed NF-κB and activated AP-1. Suppression of NF-κB activity may be due to PKC-dependent Bcl10 degradation, which decreased in response to PMA and correlated with the NF-κB activity. Regulation of cytokine expression revealed that NF-κB was essential for IL-6 but not CXCL8 expression following specific inhibition of NF-κB, without affecting AP-1 activity. Furthermore, several reports have indicated the importance of a functional NF-κB complex in zebrafish embryogenesis, where blockage of NF-κB activation resulted in a deformation of the tail. Our results indicate a suppression of apoptotic pathways following activation of inflammatory mediators in response to HK E. coli treatment. These signals acted to direct zebrafish sex differentiation towards feminization. NF-κB was shown to regulate zp2 gene expression, an indicator of oocyte development. Zebrafish sex determination was also shown to start early, prior to 16 days post fertilization. The results support the transition through a juvenile ovary stage and suggests that steriodogenesis is a consequence of sex differentiation rather than a regulatory mechanism.

Control of prescription, use and disposal of pharmaceuticals is therefore important to preserve human health, biotic processes and to avoid developmental alterations in aquatic organisms. The complexity of regulatory systems involved in inflammation suggest that there is a need to further evaluate the signalling pathways involved in order to provide a better understanding of cellular responses to manmade substances, but also to offer an insight into possible development of alternative treatments for human diseases with elevated cytokine/chemokine levels.

Keywords: Inflammation, NF-κB, cytokines, pharmaceuticals, zebrafish