EPITHEORESE KLINIKES FARMAKOLOGIAS
KAI FARMAKOKINETIKES, INTERNATIONAL
EDITION 1: 32 (2002)

Functional Role of RGS9 Protein in Morphine Analgesia and Dependence

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INTRODUCTION-AIM

Regulators of G protein signaling (RGS) negatively regulate signaling through Gi and Gq alpha subunits by accelerating the conversion of GTP to GDP. More than 20 members of the RGS family have been isolated and characterized. Previous studies have shown region specific expression of RGS family members in the rat brain (Gold et al., 1997) and transcriptional regulation by seizures and acute exposure to amphetamine (Gold et al., 1997, Burchet et al., 1998). One member of the RGS family, RGS9, was observed to be almost exclusive in brain regions that receive dense dopaminergic innervation. The cellular actions of drugs of abuse are mediated via opioid and/or dopamine receptors, both of which are known to belong to the G-protein-coupled transmembrane receptor superfamily. Using in situ hybridization and Western blotting, the present study is investigating whether treatments that can affect G protein signaling, such as chronic morphine and precipitated withdrawal can modulate RGS9 expression in the brain. Moreover this study is using RGS9 knockout mice in order to investigate the role of the particular protein in the rewarding and antinociceptive actions of morphine as well as in the development of morphine tolerance.

RESULTS AND CONCLUSIONS

Although no changes in RGS transcription were observed following these treatments, RGS9 protein levels are significantly downregulated following chronic intermittent morphine and opiate withdrawal. This observation suggests that RGS9 is regulated post-transcriptionally by modifications that alter the stability of the protein.

Behavioral studies are showing that the absence of functional RGS protein is enhancing morphine's rewarding and antinociceptive actions.

Moreover our studies are providing further evidence that the biochemical mechanism underlying tolerance and dependence are distinct, since the absence of RGS9 results in exacerbated opiate withdrawal but has no effect on the development of morphine tolerance.