EPITHEORESE KLINIKES FARMAKOLOGIAS
KAI FARMAKOKINETIKES, INTERNATIONAL
EDITION 13: 67 (1999)

Interactions of Dexamethasone and Neurotransmitter Glutamate in the Hippocampus of the Rat

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Increased concentrations of glucocorticoids in the brain are toxic. This toxicity, is maintained from several studies, is due to the observed accumulation of extracellular glutamate following physiological elevations of glucocorticoids in the hippocampus of the rat.

Most of these studies have been focused on the postsynaptic or glial participation in the events following this accumulation of extracellular glutamate; i.e. on the one hand the activation of NMDA receptors with the concomitant increase in the postsynaptic $[Ca^{2+}]i$ and production of oxygen radicals, and on the other the inhibition of the glial uptake of glutamate.

To our knowledge no studies have been carried out on the effect of glucocorticoids on the train of events that lead to the release of neurotransmitter glutamate. Therefore we studied the effect of dexamethasone (DEX) on glutamate release, a key enzyme of its biosynthesis (phosphate-activated glutaminase-PAG) and two elements of its exocytotic machinery, i.e. adenylyl cyclase (AC) activity and protein phosphorylation.

I) DEX (at physiological concentrations 10^{-6}M) significantly decreased K^+-evoked neurotransmitter glutamate release from hippocampal slices by 75%. Glutamate concentration in the superfusates was measured as described in detail.This effect was totally reversed by the glucocorticoid antagonist for their receptors RU486. This means that the DEX effect is exerted through the classical receptors. Actinomycin D did not change the DEX effect, meaning that under the experimental conditions sufficient concentrations of either mRNA or glucocorticoid receptors are present.

II) DEX (at concentrations 10^{-6} and 10^{-7}M) had no effect on PAG - the major enzyme for the biosynthesis of neurotransmitter glutamate.

III) DEX (at concentrations 10^{-5}, 10^{-6} and 10^{-7}M) significantly increased the forskolin-stimulated AC activity in a dose-dependent manner (by 133%, 139% and 29% respectively), but had no effect on the basal or the GTP-γ-S-stimulated activity. Contrary to its effect on the K^+-evoked release of neurotransmitter glutamate RU486 did not reverse the DEX effect on AC activity. This effect, it is suggested, is independent of the classical glucocorticoid receptors.

DEX affected the phosphorylation of the proteins present in both the supernatant and the membranous fractions of hippocampal homogenate. It remains to identify the fractions that are de- or phosphorylated.

ACKNOWLEDGMENTS

This work was supported by Grant 70/3/2946 from the Greek General Secretariat of Research and Technology to George Palaiologos and the University of Athens.