ENDOGENOUS ACTIVATION OF GROUP II METABOTROPIC GLUTAMATE RECEPTORS INHIBITS THE HYPOTHALAMIC-PITUITARY-ADRENOCORTICAL AXIS

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Introduction Glutamate stimulates ACTH secretion when injected icv in rodents (1). To further characterized the role of glutamate transmission on the hypothalamus-pituitary-adrenal axis activity, we studied the effect of subtype-selective ligands of metabotropic glutamate receptors (mGluRs) on mouse plasma corticosterone secretion and on in vitro CRH and ACTH release.

Materials and Methods Mice were injected i.p. with 1 mg/kg of LY379268 or LY341495, which behave as selective agonist and antagonist of mGlu 2/3 receptors, respectively, and with the non competitive mGlu 5 receptor antagonist, MPEP (5 mg/kg). Plasma corticosterone levels were determined by RIA (ICN). CRH and ACTH release was measured from isolated mouse hypothalamus and pituitary by RIA (Peninsula Laboratories), (2). Total RNA was extracted from tissues of HPA axis. PCR amplification of mGlu1-8 receptor cDNA was performed with appropriate primers. mGlu2/3 receptor protein expression was detected by Western Blot analysis.

Results Among the several mGluR ligands, only LY341495 increased corticosterone level when injected to mice. Only mGlu5 and –7 receptor mRNAs were detected in adrenal gland by RT-PCR, whereas mGlu1,-3,-4,-5,-7 and –8 receptor transcripts were detected in anterior pituitary. All transcripts (with the exception of mGlu5 and –6 receptor mRNAs) were detected in hypohyalamus. Western blot analysis showed the presence mGlu 2/3 receptor proteins only in the hypothalamus and not in the anterior pituitary. Among all mGluR ligands, only LY341495 increased CRH secretion from isolated hypothalami.

Conclusions We conclude that group-II mGlu receptors tonically regulate the HPA axis by controlling CRH secretion at hypothalamic level.