GH AND CORTISOL REBOUND RISE DURING AND FOLLOWING A SOMATOSTATIN INFUSION: STUDIES IN DOGS WITH THE USE OF A GH-RELEASING PEPTIDE (GHRP)

Rigamonti A.E., 2° anno di corso del Dottorato di in Farmacologia, Chemioterapia e Tossicologia Medica, XVI ciclo. Durata del Dottorato in anni: 4. Sede di servizio: Dipartimento di Farmacologia, Chemioterapia e Tossicologia Medica, Università di Milano, Milano.

GH releasing peptides (GHRPs), a class of small synthetic peptide and nonpeptide compounds, act on specific receptors at both the pituitary and the hypothalamic level to stimulate GH release both in animals and in humans. GHRPs, like CRH, also possess acute ACTH and cortisol-releasing activity, though the mechanisms underlying the stimulatory effect of GHRPs on the hypothalamo-pituitary-adrenal (HPA) axis are still unclear. In recent years, studies in animals and humans have provided evidence that the rebound GH rise which follows withdrawal of an infusion of SS (SSIW) is due, at least in part, to the functional activation of GHRH neurons of the recipient organism. Unexpectedly, in humans, SS infusion, at a dose inhibiting basal GH secretion, was associated with an activation of HPA axis, leading to hypothesize that this response was mediated, at least in part, by a CNS ACTH-releasing mechanism activated by the SS-induced decrease in GH secretion. Interestingly, the rebound GH rise which follows SSIW was magnified by the administration, before SS withdrawal, of a GHRP, implying that the SSIW approach could also be exploited to investigate "*in vivo*" the functional interaction in the process of GH and/or ACTH/cortisol secretion between endogenous GHRH (and/or other ACTH-releasing mechanisms) and GHRPs.
In the present study, six young beagle dogs were administered, on different occasions, at the beginning and at end of a 3-h intravenous infusion of SS or saline, a bolus of physiological saline or a GHRP compound, EP51216.
SSIW induced a GH rebound rise without affecting plasma cortisol concentrations, while withdrawal of saline infusion was ineffective on either hormone paradigm. Administration of EP51216 at the beginning of saline (SAL) infusion evoked release of both GH and cortisol, whereas EP51216 administration at the withdrawal of SAL infusion evoked somatotroph and cortisol responses which were reduced in amplitude and duration. SS infusion significantly reduced the secretion of GH elicited by EP51216 but did not affect the rise of plasma cortisol levels. Interestingly, SSIW resulted in a marked enhancement of the somatotroph and cortisol responses evoked by EP51216.
The marked rise of plasma GH levels induced by the GHRP after SSIW recalled that occurring after acute combined administration of rhGHRH and EP51216, implying that exogenously delivered GHRP had synergized with the endogenous GHRH release triggered by SSIW. In contrast, acute combined administration of GHRH and the GHRP induced a cortisol response not different from that induced by GHRP alone, indicating that endogenous GHRH release was not involved in the enhanced cortisol response ensuing EP51216 administration after SSIW. Similarly, the direct involvement of endogenous CRH could be ruled out, since iv administration of oCRH after SSIW evoked cortisol peak levels not different from those evoked by CRH at the withdrawal of SAL infusion.
In conclusion, enhancement of the GH response to EP51216 alone by SSIW to an extent reminiscent of that following combined administration of GHRH and EP61216, reinforces the view that SSIW elicits release of endogenous GHRH. Further studies are instead mandatory for a better understanding of the mechanisms underlying the enhanced cortisol response, since from now the involvement of endogenous GHRH or CRH can be ruled out.