CONTRASTING EFFECTS OF NITRIC OXIDE ON FOOD-INTAKE AND GH SECRETION STIMULATED BY A GH-RELEASING PEPTIDE (GHRP) IN YOUNG-ADULT RATS

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Based on nitric oxide (NO) involvement in the GH-releasing effect of the GH-releasing peptides (GHRPs) and the reported orexigenic activity of these compounds, we sought to evaluate the effect of the combined administration of a long-acting NO-donor, molsidomine, and/or an inhibitor of NO-synthase, N-nitro-arginine-methyl-ester (NAME), and the GHRP EP92632 on food-intake and GH secretion in rats.

Methods. In the food-intake experiments, adult Sprague-Dawley male rats underwent acute administration of: 1) EP92632 (160 µg/kg, sc); 2) molsidomine (100 mg/kg, ip); 3) EP92632 + molsidomine; 4) L-NAME (60 mg/kg, ip); 5) EP92632 + L-NAME (60 mg/kg, ip); 6) EP92632 + molsidomine + L-NAME (60 mg/kg, ip); 7) 0.9% saline (0.1 ml/kg, ip). In the neuroendocrine experiments, rats were given the same compounds according to the above reported schedule, except for the use of a lower EP92632 dose (80 µg/kg, sc).

Results. EP92632 significantly stimulated food-intake (3.4±0.6 *vs.* 2.6±0.7 g, $P < 0.01$), an effect which was further enhanced by molsidomine (6.4±0.6 g, $P < 0.01$), which had no orexigenic effect *per se*. L-NAME significantly decreased food-intake and abolished the orexigenic effect of the GHRP and the enhancing effect of molsidomine. Plasma GH levels increased significantly following administration of EP92632 ($AUC_{rGH\ 0\text{-}90}$: 18617.9±2267.8 ng/ml/min *vs.* 10267.1±1445.6 ng/ml/min, $P < 0.01$), but, in contrast to the food-intake experiments, molsidomine significantly inhibited both basal and EP92632-stimulated GH secretion (at 10, 15 and 30 min and at 30 min, respectively, $P < 0.01$ *vs.* saline + saline); moreover, NAME exerted a biphasic effect on the EP92632-stimulated GH release, being, initially, inhibitory and, then, from 45 min on, stimulatory. NAME did not affect basal GH levels but, surprisingly, combined administration of molsidomine and NAME induced a striking inhibition of both basal and the peptide-stimulated GH release ($AUC_{rGH\ 0\text{-}90}$: 4307.8±688.1 ng/ml/min; $P < 0.01$ *vs.* saline + saline; $AUC_{rGH\ 0\text{-}90}$: 14032.3±1828.3 ng/ml/min; $P < 0.01$ *vs.* saline + EP92632; respectively).

Conclusions. These data indicate that NO in the rat stimulates the GHRP-mediated effect on food-intake, but exerts a dual action, likely stimulatory at hypothalamic and inhibitory at pituitary levels, on basal and GHRPs-stimulated GH secretion.