OXYTOCIN: NEW ROLES FOR AN OLD HORMONE

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The hypothalamic hormone oxytocin (OT) exerts its biological effects by binding to a specific receptor (OTR) belonging to the G protein-coupled receptor (GPCR) family, and originally described in the uterus. More recently, the expression of OTRs structurally identical to the uterine receptors has been demonstrated in a variety of cell types, including human umbilical vein endothelial cells (HUVECs), where OT acts as a mitogen [1].
By means of chemotaxis experiments, here we show that the hormone also stimulates migration in HUVECs, in a manner comparable to VEGF. The specificity of the OT action is confirmed by the ability of OTR antagonists to inhibit the hormone's migratory effect.
Human OTRs are promiscuously coupled to $G_{\alpha q}$ and $G_{\alpha i}$. We show that in HUVECs the OT-induced migration is not affected by pertussis toxin, suggesting that the hormone effect does not depend on a G_i-coupled OTR, but most probably on an OTR-G_q coupling. In support of this hypothesis, the promigratory effect of OT is abolished by the PLC inhibitor U73122.
The PLC/Ca^{2+}/calmodulin and the PI-3-K/Akt pathways can both activate endothelial nitric oxide synthase (eNOS) with consequent NO formation. In our experiments OT can in fact phosphorylate eNOS at Ser 1177 in a PI-3-K-dependent manner. Using L-NAME and LY294002 as inhibitors of eNOS and PI-3-K respectively, we show that both NO and PI-3-K pathways are crucial for the promigratory effect of OT.
Our results indicate that OT, in addition to the previously reported mitogenic effect, can act by stimulating also the motility of endothelial cells. It might be suggested that locally produced OT can contribute *in vivo* to the activation of endothelial cells *i.e* .to the first step of new vessel formation. Since endometriosis is a pathological condition greatly substained by angiogenesis, we hypothesize that OT might play a role in the development of this disease.
To this purpose, we tested the promigratory effect of conditioned media collected from human endometrial cells obtained from biopsies of endometriotic lesions, and found a stimulatory effect on HUVEC migration. This effect was reversed by OTR antagonists in about 35% of the conditioned media tested. These results suggest that, at least in a subpopulation of patients, OT produced by endometrial cells might contribute *in vivo* to some aspects of the angiogenic process required for the development of endometriosis by promoting endothelial cell proliferation and motility.

1. Thibonnier M. et al. (1999) Endocrinology 140:1301-1309.