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Significance of orexin in the water metabolism and the regulation of vasopressin secretion

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Orexins have been described before a decade, from the lateral hypothalamic area. Orexin neurons project to multiple region in the brain, including the hypothalamic paraventricular and supraoptic nucleus, which are the main vasopressin (VP) producing cells in the central nervous system. Positive immunostaning of the orexin receptors (OX_1R and OX_2R) were also observed in these magnocellular regions. The influence of the orexins on the water metabolism has been proved, but the possible role of VP release in connection with polydipsia and polyuria has not been clarified.

The effects of the centrally administered neuropeptides orexin-A and -B on water intake and VP secretion after hyperosmotic and histamine (HA)-induced stimulus were studied *in vivo* in male Wistar rats; and the effects of monoamine (dopamine (DA), serotonin (5-HT), HA, adrenaline (ADR), noradrenaline (NADR)) and K^+ administration on VP secretion were studied *in vitro* in 13-14-day cell cultures from rat neurohypophysis (NH), and it was examined whether orexins can modify the induced VP release enhancement.

Increased water consumption was observed after the administration of both orexin-A or orexin-B. There were no changes in basal VP concentration of the plasma after the administration of different doses of the orexins. A significant increase in VP secretion was detected following HA and 2.5% NaCl administration, a moderate VP level enhancement was detected in the latter case. Centrally administered orexin-A blocked the VP level increases induced by HA or hyperosmosis. The inhibitory effects of orexin-A were prevented by specific OX_1R antagonist.

Following administration of orexin-A or orexin-B in increasing doses, significant changes were not observed in the VP levels of the supernatant media of the cell cultures from isolated rat NH. VP level substantially increased after NADR, ADR or 5-HT treatment, while the enhancing effects of DA, HA or K^+ administration were more moderate. Preincubation with orexin-A or orexin-B reduced the monamine-induced VP level increases, except in the case of DA. The decreases were significant, but the VP concentrations of the supernatant media remained high above the control level. There was no significant difference in the decreasing effect between orexin-A and orexin-B. Orexins had no influence on the VP level increase induced by K^+, which causes non-specific, receptor-independent hormone secretion. Orexin-A or -B did not induce any changes in VP release when administered after the monoamine-treatments. OX_1R antagonist treatment avoided the effects of the orexin-A preincubation on monoamine-induced VP level enhancements.

According to our results we concluded that: 1. Orexin-A or orexin-B can cause polydipsia. 2. Orexin-A (when administered i.c.v. *in vivo*) and both orexin-A or orexin-B (by preincubation in cell cultures) can reduce the induced VP release enhancement. 3. The effects of orexin-A on the water metabolism or on the VP level increases (either histamine- or osmotic-induced *in vivo*, or monoamine-induced in NH cell cultures) are mediated through the OX_1R. 4. The interactions of the orexin systems regarding VP secretion occur both at hypothalamic and at the level of the posterior pituitary.

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Genetic analysis of the FMRFamide-related neuropeptides and their specific receptors in *Drosophila melanogaster*

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Neuropeptides are produced and secreted by specific neurons in all Metazoan organisms. They steer important processes like reproduction, feeding, behaviour, circadian rhythm, etc. from worms to humans. They are also very important regulators of insect life. *Drosophila melanogaster* has 45 known neuropeptides. We use the excellent genetic system of the fruitfly to perform a systematic genetic analysis of the functions exerted by the FMRFa-related (FaRP) group of peptides (FMRFa, Dms, Dsk, NPF, sNPF) and their GPCR receptors (FR, Dms-R1 and -2, Dsk-R1 and -2, NPFR, sNPFR).

We have built a RNAi-based genetic system in which the FMRFa-related genes and their specific receptors can be silenced in pairwise combinations. For this we used the RNAi transgenes available from stock centers. The RNAi transgenes can be driven by the Gal4-inducible UAS promoter. Using the Act5-Gal4 „driver" which induced an ubiquitous and continuous expression of the RNAi double-stranded RNA, silencing of the *FMRFa, Dms, Dms-R1* and *Dsk-R2* genes resulted in complete lethality while the others remained viable. The lethal effect