A NOVEL APPROACH TO MODELING MENOPAUSAL SYMPTOMS AND THE ROLE OF THE OREXIN SYSTEM

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Menopausal symptoms become prevalent in conditions associated with depletion of estrogens [e.g., ovariectomy surgery or with breast cancer treatments that block estrogen activity (e.g., tamoxifen or aromatase inhibition therapy)]. The primary menopause associated symptom is cutaneous vasodilation “hot flashes”, but also includes sleep and mood disruption (Freeman et al., 2005; Seritan et al., 2010). Although the cause of menopausal symptoms is poorly understood, it is well-established that the hypothalamus: 1) plays a critical role in thermoregulation, sleep wake activity and emotional responses; and 2) has high and fairly exclusive expression of both estrogen α and β receptors (Laflamme et al., 1998). A recently discovered neuropeptide called Orexin (ORX) is exclusively synthesized in the perifornical hypothalamus (PeF). This neuropeptide plays a critical role in arousal, anxiety (Johnson et al., 2010), and body temperature regulation (Rusyniak et al., 2011), but is also severely elevated in the brain of postmenopausal women (El-Sedeek et al., 2010) and reduced in control subjects following estrogen replacement.

Therefore, loss of normal inhibitory control by estrogens of the ORX system may lead to menopausal-related symptoms, and ORX antagonists could constitute a potential novel treatment strategy for adverse menopausal symptoms. In support of this hypothesis, ovariectomized (OVEX), female rats, compared to sham controls, had significantly greater anxiety at baseline which was blocked by administration of an ORX1 receptor (ORX1R) antagonist (SB334867, 25mg/kg ip) or estrogen replacement. Administration of a sub-threshold dose of FG-7142 (a partial inverse $GABA_A$ receptor agonist, 3mg/kg ip) caused higher (~6°C) and longer tail skin flushes in OVEX rats, which was attenuated with similar pretreatment with an ORX1R antagonist or with estrogen replacement. These results indicate a novel role for both the GABA and ORX systems in menopausal symptoms and further research aims to elucidate the mechanisms of dysfunction of these systems in the menopausal state.

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