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P20. OX-A-INDUCED ENHANCEMENT OF 2-AG LEVELS IN DIFFERENT BRAIN AREAS OF OBESE ob/ob MICE

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Orexin-A (OX-A) is a neuropeptide expressed by a small number of neurons of the lateral hypothalamus (LH), a key regulatory center of feeding and sleep-wake functions in the brain. According to the involvement of OX-A in the control of arousal, stress- and reward-related behaviors, OX-A projections are widely distributed throughout the central nervous system including hypothalamic nuclei [arcuate (ARC), supra-chiasmatic (SCN), ventro-medial, (VMN), dorsomedial (DMN) and periventricular (PVN)], cortex, nucleus accumbens, hippocampus, ventrotegmental area (VTA) and different locus in the brainstem. An endocannabinoid-mediated disinhibition of OX-A expressing neurons occurs in the brain of leptin signaling-defective obese ob/ob mice, concurrently with elevation of OX-A trafficking and release to the different LH target areas. By binding OX-1R receptors, OX-A has been found to promote the synthesis of 2-arachidonoylglycerol (2-AG), the main endocannabinoid regulating synaptic transmission in a retrograde manner by inhibiting the release of GABA or glutamate at presynaptic cleft. Here we provide morphological and anatomical evidence showing enhancement of OX-A trafficking into fibers projecting to many different LH target areas in concurrence with elevation of 2-AG content by biochemical LC-MS quantification of endocannabinoid levels in obese ob/ob mice compared to wild-type mice. These effects result in a change of excitatory/inhibitory balance in different brain regions of obese mice, with functional outcomes on the synaptic plasticity of neuronal network regulating stress-, reward-, sleep-wake- and arousal-related behaviours, which were prevented by i.p. injection of leptin and reversed by antagonism of OX-1R with SB334867 in ob/ob mice.