P03-384

OREXINS: AN ADDICTING LESSON IN THE TREATMENT OF DEPENDENCE

P.Y. Xiu[1,2], S. Masand[2,3], M. Agius[4,5], R. Zaman[4,5]

[1]School of Clinical Medicine, [2]Department of Pharmacology, University of Cambridge, Cambridge, [3]School of Medicine, King's College London, London, [4]Department of Psychiatry, University of Cambridge, Cambridge, [5]Psychiatry, Bedfordshire and Luton Partnership Trust, Bedford, UK

Introduction: Orexin (hypocretin) neuropeptides are produced by a cluster of neurons in the hypothalamus. They are central to a variety of functions, including promoting arousal and sleep, feeding and metabolism, addiction and regulating motivation. Deficiencies and over-activation in each of these functional systems have a great impact on the daily lives of millions. We need to apply the lessons learned from the current knowledge to potentially modulate them by pharmocological interference in a clinical setting.

Objectives: To analyse current experimental literature on the orexin pathways in reward and addiction; assessing potential molecular targets for pharmacological interference; reviewing clinical evidence already available.

Methods: PubMed - searched with MeSH term “orexin” or "hypocretin”, with additional terms; "addiction", "stress", "relapse", "VTA", "Nucleus Accumbens", "treatment".

Results: We outline all the important parmacological targets through which orexins have their effect via different downstream effectors. Moreover we propose that since orexins have an important interplay with corticotrophin-releasing-factor (CRF) in the role of stress-mediated drug-seeking behaviour; it is a ripe target for intervention. Novel, orally administered orexin antagonists, have potential to promote sleep and attenuate reward circuitry, however only within narrow therapeutic ranges.

Conclusion: Orexin functions are so wide-ranging that systemic orexin antagonism would cause detrimental side-effects, unless low enough doses are applied. Therefore molecule-specific and location-specific down-stream targeting will be required, using knowledge of experimentally elucidated molecular mechanisms. Various orexin agonists and antagonists are available, and by understanding their mechanism of interaction we can potentially use them as a model for future treatments of addiction.

https://doi.org/10.1016/S0924-9338(10)70990-1 Published online by Cambridge University Press