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Plenary Lecture

Orexin / hypocretin receptor antagonists and agonists in neuropsychiatric disordersDaniel Hoyer*Department of Pharmacology and Therapeutics, School of Biomedical Sciences, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne*

The physiopathological roles of orexins/hypocretins are supported by preclinical and clinical studies. Orexin A and B (hypocretins 1 and 2) and their two receptors (OX1R and OX2R) affect arousal, sleep/wake regulation, reward and stress. The absence of orexin producing cells in the lateral hypothalamus (LH) and of orexin in the CSF, results in narcolepsy with cataplexy (narcolepsy type I). Orexin KO or double OX1R / OX2R KO mice display narcolepsy/cataplexy, whereas OX2R KO and OX1R KO mice have moderate or no sleep phenotype. These features triggered drug discovery programmes for the treatment of insomnia and other disorders. Dual OX1R / OX2R antagonists (DORAs) are close to or marketed. Suvorexant (Belsomra®) and Lemborexant (Dayvigo®) are the first registered orexin hypnotics. DORAs promote sleep primarily by increasing REM (rapid eye movement) sleep, with little effect on NREM (non-rapid eye movement), especially slow wave sleep (SWS), although the primary target mediating sleep by DORAs and other OXR antagonists is the OX2R. We shall briefly review preclinical and clinical data of OXR antagonists and agonists in various neuropsychiatric diseases. REM sleep enhancement by DORAs provides opportunities to treat specific neurological disorders, whereas OX2R antagonists such as Seltorexant (JNJ-54717793), have broader applications, by promoting balanced sleep and antidepressant effects, whereas OX1R antagonists may be indicated in panic/anxiety or addiction. The development of OXR agonists is in very early stages. In preclinical models, OXR agonists produce arousal and have anti narcolepsy/cataplexy effects as expected. In the clinic, only peptide agonists have been tested so far, with very limited success. In summary, OXR antagonists and agonists represent an exciting new class of neuropsychiatric treatments.