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Insomnia and beyond - Exploring the therapeutic potential of orexin receptor antagonists Michel Alexander Steiner, Christopher J Winrow, 2014-11-11 Orexin hypocretin neuropeptides produced by a few thousand neurons in the lateral hypothalamus are of critical importance for the control of vigilance and arousal of vertebrates from fish to amphibians birds and mammals Two orexin peptides called orexin A and orexin B exist in mammals They bind with different affinities to two distinct widely distributed excitatory G protein coupled receptors orexin receptor type 1 and type 2 OX_R 1 2 The discovery of an OX_R mutation causing canine narcolepsy the narcolepsy like phenotype of orexin peptide knockout mice and the orexin neuron loss associated with human narcoleptic patients laid the foundation for the discovery of small molecule OX_R antagonists as novel treatments for sleep disorders Proof of concept studies from Glaxo Smith Kline Actelion Pharmaceuticals Ltd and Merck have now consistently demonstrated the efficacy of dual OX_R antagonists DORAs in promoting sleep in rodents dogs non human primates and humans Some of these antagonists have completed late stage clinical testing in primary insomnia Orexin drug discovery programs have also been initiated by other large pharmaceutical companies including Hoffmann La Roche Novartis Eli Lilly and Johnson Johnson Orexins are increasingly recognized for orchestrating the activity of the organism s arousal system with appetite reward and stress processing pathways Therefore in addition to models of insomnia pharmacological effects of DORAs have begun to be investigated in rodent models of addiction depression and anxiety The first clinical trials in diabetic neuropathy migraine and depression have been initiated with Merck s MK 6096 www.clinicaltrials.gov Whereas the pharmacology of DORAs is established for their effects on wakefulness pharmacological effects of selective OX_R 1 or OX_R 2 antagonists SORAs have remained less clear From an evolutionary point of view the OX_R 2 was expressed first in most vertebrate lineages whereas the OX_R 1 is believed to result from a gene duplication event when mammals emerged Yet both receptors do not have redundant function Their brain expression pattern their intracellular signaling as well as their affinity for orexin A and orexin B differs During the past decade most preclinical research on selective OX_R 1 antagonism was performed with SB 334867 Only in recent years other selective OX_R 1 and OX_R 2 antagonists with optimized selectivity profiles and pharmacokinetic properties have been discovered and phenotypes of OX_R 1 and OX_R 2 knockout mice were described The present Research Topic referred to in the Editorial as special topics issue comprises submissions of original research manuscripts as well as reviews directed towards the neuropharmacology of OX_R antagonists The submissions are preclinical papers dealing with dual and or selective OX_R antagonists that shed light on the differential contribution of endogenous orexin signaling through both OX_Rs for cellular physiological and behavioral processes Some manuscripts also report on convergence or divergence of DORA vs SORA effects with phenotypes expressed by OX_R 1 or OX_R 2 knockout animals Ultimately these findings may help further define the potential of DORAs and SORAs in particular therapeutic areas in insomnia and beyond insomnia Genetic Engineering News ,1998 **Anticancer**

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