1. Record Nr. UNINA9910136406903321

Autore	Michel Alexander Steiner
Titolo	Insomnia and beyond - Exploring the therapeutic potential of orexin receptor antagonists
Pubbl/distr/stampa	Frontiers Media SA, 2014
Descrizione fisica	1 online resource (219 p.)
Collana	Frontiers Research Topics
Soggetti	Neurology and clinical neurophysiology
Lingua di pubblicazione	Inglese
Formato	Materiale a stampa
Livello bibliografico	Monografia

Sommario/riassunto

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 (OXR-1/2). The discovery of an OXR 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 OXR 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 OXR 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 OXR-1 or OXR-2 antagonists (SORAs) have remained less clear. From an evolutionary point of view, the OXR-2 was expressed first in most vertebrate lineages, whereas the OXR-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 OXR-1 antagonism was performed with SB-334867. Only in recent years, other selective OXR-1 and OXR-2 antagonists with optimized selectivity profiles and pharmacokinetic properties have been discovered, and phenotypes of OXR-1 and OXR-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 OXR antagonists. The submissions are preclinical papers dealing with dual and/or selective OXR antagonists that shed light on the differential contribution of endogenous orexin signaling through both OXRs for cellular, physiological and behavioral processes. Some manuscripts also report on convergence or divergence of DORA vs. SORA effects with phenotypes expressed by OXR-1 or OXR-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.