Available online at www.sciencedirect.com

SciVerse ScienceDirect

Current Opinion in Neurobiology

Ascending orexinergic pathways and alcohol-seeking

Robyn Mary Brown[1,2,3] and Andrew John Lawrence[1,3]

Orexin (hypocretin) containing neurons reside in discrete regions of the lateral hypothalamus from where they innervate the entire neuroaxis. Via actions upon orexin receptors (OX_1 and OX_2), the orexin peptides (orexin A and orexin B) are thought to play a role in ethanol consumption and seeking. While a role for OX_1 receptors in these behaviours is established, the case for OX_2 receptors is less clear at present, although recent data certainly support an involvement of OX_2 receptors in ethanol consumption. In terms of circuitry, orexin receptors the ventral tegmental area appear to contribute to ethanol consumption. Other loci remain to be characterised, and we suggest prefrontal cortical orexin receptors deserve attention in this respect.

Addresses
[1] Florey Institute of Neuroscience & Mental Health, University of Melbourne, Parkville, Australia
[2] Department of Neurosciences, Medical University of South Carolina, Charleston, SC, United States
[3] Centre for Neuroscience Research, University of Melbourne, Parkville, Australia

Corresponding author: Lawrence, Andrew John (andrew.lawrence@florey.edu.au, andrewjl@unimelb.edu.au)

Current Opinion in Neurobiology 2013, **23**:467–472

This review comes from a themed issue on **Addiction**

Edited by **Barry Everitt** and **Ulrike Heberlein**

For a complete overview see the Issue and the Editorial

Available online 25th March 2013

0959-4388/$ – see front matter,

http://dx.doi.org/10.1016/j.conb.2013.02.014

Introduction

Orexins (hypocretins) are a relatively recently characterised family of neuropeptides which, among various functions, play a role in reward processing and drug-seeking behaviour. Despite their restricted origins, being synthesised exclusively in distinct regions of the lateral hypothalamus (LH), orexins exhibit a diffuse pattern of expression, with projections extending in ascending and descending, as well as dorsal and ventral directions [1]. Since the first discovery that orexins play a role in reward-seeking [2] the orexin projection targeting the ventral tegmental area (VTA) has been extensively studied in this context [3,4••,5]. This review will focus on recent progress, which is beginning to delineate the specific circuitry, including regions outside the VTA projection, which contribute to alcohol consumption and alcohol-seeking behaviour.

Orexin receptors

Orexins elicit their effects via two G-protein-coupled receptors: the orexin-1 (OX_1) receptor and orexin-2 (OX_2) receptor. OX_1 receptors appear to exclusively couple via the G_q subclass of G proteins whereas OX_2 receptors can couple to G_q, G_i and $G_{i/o}$ subclasses [6]. Both orexin A and orexin B display equal affinity for the OX_2 receptor, whereas orexin A preferentially binds to the OX_1 receptor [6]. Consistent with the diffuse pattern of expression of orexin-containing neurons, OX_1 and OX_2 receptors are widely distributed within the brain [7] showing overlapping yet also divergent patterns of expression. OX_1 receptors are highly expressed in cortical regions, bed nucleus of the stria terminalis and brainstem regions such as the locus coeruleus. By contrast, OX_2 receptors are comparatively more densely expressed in nucleus accumbens (NAc), hypothalamic regions and medial thalamic groups (PVT). The VTA contains moderate levels of both receptors [7,8]. Collectively, these differences in signalling, distribution and binding affinity for the orexin ligands indicate a possible divergence of function between the two orexin receptors. Indeed, the majority of evidence to date indicates that arousal is most closely associated with activation of OX_2 receptors and reward with OX_1 receptor activation (for review see [9]). However, recent evidence suggests OX_2 receptors may also play a role in mediating the rewarding properties of drugs of abuse, particularly alcohol.

The role of orexins in ethanol reward and ethanol-seeking

In 2006 orexin signalling was first implicated in the reinforcing properties of ethanol and cue-elicited ethanol seeking [9]. The OX_1 receptor antagonist SB-334867 reduced self-administration of ethanol as well as reinstatement of ethanol-seeking induced by both visual and olfactory cues in iP rats. Subsequently, similar effects have been demonstrated with stress-induced reinstatement in Long-Evans rats [10] and reinstatement elicited by discriminative cues in Wistar rats [11•], though in a different paradigm of ethanol-seeking SB-334867 had no effect in female rats [12]; an observation consistent with cocaine data [13]. These functional data are supported by the observation that cue-induced reinstatement of alcohol-seeking is associated with activation of orexin-containing neurons [14]. In addition, a positive correlation between the activation of orexin neurons and context-driven renewal of ethanol-seeking has been reported [15]. Subsequently this evidence has been expanded to include the observation that SB-334867 abolishes cue-induced reinstatement of alcohol-seeking both immediately after extinction as well as after an extended period of

abstinence following extinction [16••]. Thus, overall, the role for OX_1 receptor signalling across multiple modalities of ethanol-seeking is in support with findings regarding other drugs of abuse and supports a role for OX_1 receptors in the learning of drug-cue associations and drug-seeking elicited by external stimuli [17,18].

Evidence suggests that the role of OX_1 receptors in mediating the primary rewarding properties of ethanol is relatively more complex. A recent study failed to replicate the original findings that OX_1 receptor antagonism reduces self-administration of ethanol [9]. This seemingly negative study was performed in Wistar rats with a different OX_1 receptor antagonist, SB-408142, which also had no impact on ethanol-induced CPP [19••]. These data were however consistent with findings that SB-334867 reduced expression of a weak, but not strong, CPP to ethanol [20]. To clarify the situation we replicated our original study over a range of doses of SB-334867 [21•]. A low dose of SB-334867 (5 mg/kg) had a significantly greater effect on responding for ethanol compared to sucrose. Moreover, this dose of SB-334867 attenuated responding on a progressive ratio schedule for ethanol but not sucrose [21•], implicating a role for OX_1 receptors in the motivational properties of ethanol to a greater extent than that for sucrose. Given the different strains of rats in these studies (in particular low vs. high preference for ethanol) as well as the selective effect of SB-334867 on breakpoint for ethanol, it could be postulated that OX_1 receptors are recruited selectively when levels of ethanol consumption or motivation to consume ethanol is high. This is supported by the observation that SB-334867 selectively reduces ethanol consumption and preference in high (but not low) ethanol-preferring Sprague-Dawley rats [22•]. Indeed, high-saccharin preferring rats, which also consume more ethanol than low-saccharin preferring rats, have a higher number of orexin-positive cells in the LH than their low-saccharin preferring counterparts [23]. In addition, rats predicted by to be high ethanol consumers have altered orexin peptide levels in the perifornical region of the LH [24].

In contrast to OX_1, there are relatively little data on the role of OX_2 receptors in ethanol-seeking, though a recent study has demonstrated that blockade of OX_2 receptors reduced primed reinstatement of an ethanol-conditioned place preference (CPP) [19••]. This is in contrast to cocaine data which showed no impact of the OX_2 receptor antagonist 4-PT on reinstatement of cocaine-seeking [25]. The impact of OX_2 receptor antagonism on reinstatement of ethanol-seeking is yet to be systematically determined. It does appear, however, that a role for OX_2 receptor signalling exists in ethanol reward as administration of the OX_2 receptor-selective antagonist JNJ-10397049 reduced operant responding for ethanol (but not saccharin) as well as an ethanol-conditioned place preference in rodents [19••]. This was independent of any sedative effects and JNJ-10397049 did not impact motor impairments induced by ethanol. In addition, systemic administration of the dual OX_1 and OX_2 receptor antagonist Almorexant decreased responding for ethanol and sucrose in Long-Evans rats, an effect that was restricted to ethanol when the same drug was injected into the VTA [4••]. A role for OX_2 receptors in mediating the rewarding properties of ethanol is consistent with a recent study whereby blockade of OX_2 receptors reduced morphine-induced CPP [26].

Possible sites of action

A number of recent studies have improved our knowledge of where and how orexin signalling can modulate consumption of ethanol. These studies build upon previous data, which showed microinjections of orexin-A into the paraventricular nucleus and LH (but not NAc shell) increased ethanol self-administration in Sprague-Dawley rats [27]. Intra-LH injections of either NMDA or AMPA enhanced the drinking of, and preference for, ethanol and simultaneously increased local expression of orexin in the LH and perifornical area, implicating orexin in this process [28•]. These findings suggest that glutamatergic inputs to orexin neurons may contribute to ethanol-seeking. From an efferent perspective, the dual OX_1/OX_2 receptor antagonist almorexant administered into the VTA reduced self-administration of ethanol, implicating orexin signalling this midbrain region in ethanol reinforcement [4••].

Orexin signalling in VTA

The finding that orexin signalling within the VTA regulates the reinforcing properties of ethanol is consistent with other drugs of abuse such as cocaine. The VTA has been shown to be a site of action for orexin regulation of both discrete and discriminative cue-induced cocaine-seeking as well as motivation to self-administer cocaine; the same is not the case for reinstatement elicited by priming or stress [2,3,5,29•,30]. This suggests that orexin signalling in VTA is particularly important for the integration of drug-cue associations. A role for orexin projections to the VTA in ethanol-seeking behaviour (as opposed to consumption) is yet to be confirmed.

VTA orexin signalling has the capacity to influence ethanol reinforcement in a number of ways. Thus, orexins increase tonic and burst firing of dopamine neurons in the VTA [31], and blockade of OX_1 receptors reduces dopamine cell firing [32]. Despite a study suggesting that orexin innervation of VTA dopamine neurons is relatively sparse, intra-VTA administration of SB-33486 reduces both basal and cocaine-induced dopamine release in the NAc [29•,33,34]. This VTA-NAc orexin–dopamine interaction is supported by behavioural evidence, which shows that intra-VTA orexin A induces a CPP which is dependent on NAc dopamine signalling [35].