Pharmacology, Biochemistry and Behavior 134 (2015) 31–34

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Mini-review

Do Orexins contribute to impulsivity-driven binge consumption of rewarding stimulus and transition to drug/food dependence?☆

Manuel Alcaraz-Iborra [a], Inmaculada Cubero [a,b,*]

[a] Departamento de Neurociencia y Ciencias de la Salud, Universidad de Almería, Almería 04120, Spain
[b] Carrera de Psicología, Facultad Ciencias Jurídicas y Sociales, Universidad Autónoma de Chile, Santiago de Chile, Chile

ARTICLE INFO

Article history:
Received 2 December 2014
Received in revised form 10 March 2015
Accepted 13 April 2015
Available online 28 April 2015

Keywords:
Orexins
Compulsivity
Impulsivity
Binge consumption
The addiction cycle

ABSTRACT

Orexins (OX) are neuropeptides synthesized in the lateral hypothalamic region which play a fundamental role in a wide range of physiological and psychological functions including arousal, stress, motivation or eating behaviors. This paper reviews under the addiction cycle framework (Koob, 2010), the role of the OX system as a key modulator in compulsivity-driven consumption of rewarding stimulus including ethanol, palatable food and drugs and their role in impulsivity and binge-like consumption in non dependent organisms as well. We propose here that drug/food binge-like consumption in vulnerable organisms increases OX activity which, in turn, elicits enhanced impulsivity and further impulsivity-driven binge consumption in a positive loop that would promote compulsive-driven binge-consumption and the transition to drug/food disorders over time.

Contents

1. Introduction . . . 31
2. The Orexin system . . . 32
2.1. OXr1 signaling modulates compulsive consumption of rewarding stimulus: a role for OX in the later stage of the addiction cycle . . . 32
2.2. OXr1 signaling modulates impulsivity and binge-like consumption of rewarding stimulus: a role for OX in the early stage of the addiction cycle 32
3. Concluding remarks and future directions . . . 33
Acknowledgments . . . 33
References . . . 33

1. Introduction

Drug addiction has been conceptualized as a disorder that involves elements of both impulsivity and compulsivity, in which impulsivity, a core deficit in substance abuse disorders (Allen et al., 1998), has been typically defined as "rash and spontaneous without forethought of negative consequences" (Dawe and Loxton, 2004) while compulsivity has been understood as a "perseveration of responding in the face of adverse consequences or perseveration in the face of incorrect responses in choice situations" (Koob, 2013). Collapsing impulsivity and compulsivity yields a composite addiction cycle comprising three stages: a binge-intoxication phase driven and characterized by the rewarding properties of the drug, a withdrawal phase accompanied by a negative emotional state as the acute rewarding drug properties wear off, and a preoccupation and anticipation phase that precedes renewed drug intake (Koob and Volkow, 2010). The transition governing this cycle is dominated by impulsivity at the early stages and impulsivity combined with compulsivity at the later stages (Koob and Volkow, 2010). The three stages are conceptualized as interacting with each other, becoming more intense, and ultimately leading to the pathological state known as addiction (Koob and Volkow, 2010).

Similarly to drug addiction, many scientists have proposed that obesity and eating disorders might share the same dynamic and properties

☆ Authors' contributions: Both authors have contributed equally to write the manuscript.

* Corresponding author at: Departamento de Neurociencia y Ciencias de la Salud, Universidad de Almería, Almería 04120, Spain.
E-mail addresses: manuel.alcaraziborra@gmail.com (M. Alcaraz-Iborra), icubero@ual.es (I. Cubero).

http://dx.doi.org/10.1016/j.pbb.2015.04.012
0091-3057/

of drug addiction (Davis and Claridge, 1998; Riva et al., 2006; Trinko et al., 2007; Volkow et al., 2008). Dr. Bartley Hoebel and cols. have been one of the earlier researchers who hypothesized that repetitive binge-like intake of sugar and maybe other palatable foods could also be governed by the main physiological and psychological components of drug addiction disorders (Avena et al., 2008). Thus, sugar-bingeing, sugar-withdrawal, sugar-craving and sugar/drugs cross-sensitization are all effects given operational definitions and successfully tested in several behavioral and pharmacological studies (Avena et al., 2001; Avena et al., 2008). Moreover, prolonged binge eating, also defined as "food addiction" (Avena et al., 2001), has been well-established as a compulsive behavior, a key feature of bulimia nervosa or binge-eating disorder, and has been observed in obese patients as described by the *Diagnostic Statistical Manual V* (APA, 2013).

Dr. Thiele and cols. have recently proposed that overlapping neurobiological systems may be involved in early and later stages of ethanol addiction (Lowery-Gionta et al., 2010; Thiele and Navarro, 2014). The hypothesis holds that some of the neurochemical systems having a key role in addictive stages might be recruited early in time during the first stages of the addiction cycle in non-dependent organisms showing binge-like consumption (Lowery-Gionta et al., 2010; Thiele and Navarro, 2014). Consistent with the idea, they have provided compelling evidence supporting the role of Corticotropin-Releasing Factor (CRF) (a peptide known to be involved in ethanol dependence) (Roberto et al., 2010) in ethanol binge-drinking in "non-dependent" animals (Lowery-Gionta et al., 2010).

We review here evidence supporting the exciting idea that OX are also relevant peptides involved both in early and later dependent stages in the cycle of addiction. We propose that repetitive episodes of binge-like consumption of rewarding stimulus in vulnerable, non dependent animals, enhance OX transmission in a positive loop that triggers increased impulsive behavior, which in turns leads to continued binge-like consumption, finally favoring the transition from non dependent/impulsive-driven binge-consumption to compulsive consumption and addiction over time.

2. The Orexin system

Orexin (OX), a hypothalamic neuropeptide produced in a small population of neurons located in the dorsomedial–perifornical hypothalamic area (DMH/PeF) and in the lateral hypothalamic nucleus (LH), consists of two forms, Orexin A and B (OX-A and OX-B), containing 33 and 28 amino acids respectively and binding to two G-protein coupled receptors, OX receptor 1 (OXr1) and OX receptor 2 (OXr2) (de Lecea et al., 1998; Sakurai et al., 1998). OX cells have extensive projections to several regions of the central and peripheral nervous system such as spinal cord, brainstem, hypothalamus, limbic system, vagus nerve and some cortical areas (Xu et al., 2013). Consistent with the widespread projections of the orexigenic peptide, the orexin system has been implicated in several physiological and psychological functions, including regulation of sleep (Ma et al., 2014; Tabuchi et al., 2014), energy metabolism (Burdakov and Alexopoulos, 2005), arousal (Tsujino and Sakurai, 2013), neuroendocrine responses to stress (Tsujino and Sakurai, 2013; Furlong et al., 2009), drug addiction (Arias-Carrión et al., 2014; Mahler et al., 2012), motivational regulation (Mahler et al., 2014) and eating behaviors (Tsujino and Sakurai, 2013).

OXr1 and OXr2 are differentially distributed throughout the mammalian brain; while OXr1 is mainly expressed in prefrontal and infralimbic cortex, hippocampus, paraventricular thalamic nucleus, ventromedial hypothalamic nucleus, dorsal raphe nucleus and locus coeruleus (Marcus et al., 2001), OXr2 is prominently expressed in cerebral cortex, septal nuclei, hippocampus, medial thalamic groups, raphe nuclei, and many hypothalamic nuclei including the tuberomammillary nucleus, dorsomedial nucleus, paraventricular nucleus and ventral premammillary nucleus (Marcus et al., 2001). According to this segregated distribution, there is growing evidence showing that multifaceted roles of orexin may be distributed throughout the function of each receptor (Sakurai, 2014). In this regard, while OXr2 has been proposed to be a major player in the regulation of the sleep–wakefulness cycle and arousal (Li et al., 2014), there is now growing acceptance that OXr1 may be mainly involved in modulating motivation for highly salient rewards (Mahler et al., 2012; Cason et al., 2010).

2.1. OXr1 signaling modulates compulsive consumption of rewarding stimulus: a role for OX in the later stage of the addiction cycle

The OX system is growing as a key factor regulating compulsive consumption of rewarding stimulus at later stages of the addiction cycle, those governed by pathological compulsive craving and relapse (Boutrel et al., 2010; Pich and Melotto, 2014). Pharmacological evidence has consistently shown a role for OX signaling in drug sensitization, drug seeking behavior and withdrawal syndrome in rodents exposed to ethanol, nicotine, morphine or cocaine (Mahler et al., 2012; Boutrel et al., 2013). Intra-VTA microinjection of OX-A produced a renewal of morphine-induced conditioned place preference, while administration of the OXr1 antagonist SB-334867 decreased the expression of conditioned place preference to morphine (Harris et al., 2005). Likewise, the highly selective OXr1 antagonist GSK 1059865 significantly blunted cocaine induced conditioned place-preference (Gozzi et al., 2011); SB-334867 blocked the acquisition of cocaine-induced behavioral sensitization and potentiation of excitatory currents induced by cocaine in VTA dopamine neurons (Borgland et al., 2006), inhibited cocaine seeking (Smith et al., 2010) and attenuated stress-induced reinstatement of cocaine (Boutrel et al., 2005). Additional data showed that SB-334867 inhibits cue-induced reinstatement of ethanol (Lawrence et al., 2006) and ethanol seeking (Richards et al., 2008). By contrast, systemic administration of the OX2R antagonist TCS-OX2-29 was unable to attenuate reinstatement of extinguished responding for cocaine (Smith et al., 2009) and had no impact on cue-induced reinstatement of ethanol seeking (Brown et al., 2013). Adding complexity to the OX2r function, the same OXr2 antagonist significantly suppressed acquisition and expression of conditioned place preference to morphine in naïve and dependent mice (Tabaeizadeh et al., 2013), indicating that more studies are needed to clarify the specific OXr2 involvement in compulsive drug intake.

The OX system has also been recently involved in compulsive eating, food seeking behavior and food craving associated to food restriction (Pich and Melotto, 2014). The OX antagonist SB-334867 inhibited the expression of conditioned place preference to high fat food when administered into the fourth ventricle (Kay et al., 2014) and decreased fructose consumption by rats in an Intermittent Access Model (IAM) that triggers binge-like consumption (Rorabaugh et al., 2014). A recent study showed that inhibiting the LH–VTA pathway reduces compulsive sucrose seeking but not food consumption in hungry mice, in a partial Reinforcement Sucrose-Retrieval Task (Nieh et al., 2015). Further, Piccoli and cols. have recently (2012) evidenced a key role for OX in the expression of excessive drive produced by craving associated to food restriction (Piccoli et al., 2012; for a review see Pich and Melotto, 2014). The authors showed that SB-334867 inhibit compulsive eating behavior in rats exposed to chronic stress induced by food restriction, while it was unable to inhibit highly palatable food intake in control animals unexposed to cyclic food restriction (Piccoli et al., 2012). Further, Piccoli and cols. reinforced the functional dichotomy of OX receptors showing that the dual orexin receptor DORA SB-649868, but not the selective OXr2 antagonist JNJ-10397049, reduced compulsive food overconsumption (Piccoli et al., 2012), confirming a key role for OXr1 signaling in compulsive eating (Pich and Melotto, 2014).

2.2. OXr1 signaling modulates impulsivity and binge-like consumption of rewarding stimulus: a role for OX in the early stage of the addiction cycle

Binge-like consumption episodes, a typical behavior exhibited during the early stages of the addiction cycle, have been extensively