Orexin signaling promotes initial alcohol consumption

Orexins (orexin-A, orx-A and orexin-B, orx-B) are neuropeptides expressed exclusively in hypothalamic neurons of the lateral hypothalamus and perifornical area. They mediate their effects through activation of two G-protein coupled receptors, the orexin-1-receptor (Orx1R) and orexin-2-receptor (Orx2R). Orx-A binds to both receptors with the same affinity whereas orx-B only binds to Orx2R. Both the fibers containing orexins and their receptors are found along the neuroaxis with a particularly intense localization in structures related to reward and motivation.

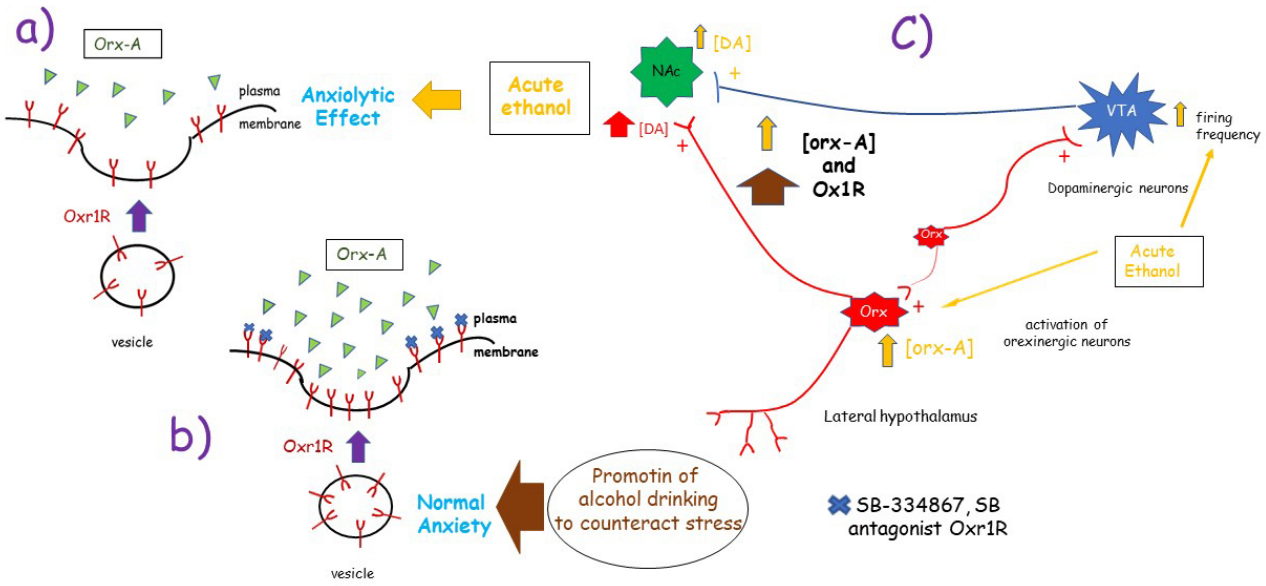

Fig. 1. A hypothetical cellular model for the action of acute ethanol intake on anxiety, orexin-A (orx-A) levels, and orexin 1 receptor (Orx1R) density, specifically in the nucleus accumbens (NAc), an area of the brain involved in the regulation of motivation and reward for drugs of abuse. (a,c) Acute ethanol increases both orx-A levels and Orx1R density, which may mediate the anxiolytic effect of alcohol. However, exposure to ethanol associated with damage to Orx1R signaling (SB) reverses the anxiolytic effect, leading to a greater increase in Orx1R density and improving orx-A concentration, promoting alcohol consumption to counteract stress (b,c).

Initially, they were involved in narcolepsy/cataplexy and arousal behaviors. Subsequent studies showed that orexins play a key role in addictive processes, such as alcohol-seeking behavior, reinstatement of stress-induced alcohol self- administration, and relapse from drug use. Orexins have been widely reported to stimulate dopamine (DA) transmission in the ventral tegmental area (VTA) and nucleus accumbens (NAc) by enhancing drug-of-abuse-induced DA release (Fig. 1c) However, little is known about the role they play in motivation in initial alcohol consumption.

The use of alcohol is known to induce a relaxing effect known as anxiolytic effect (Fig. 1a,c). This effect can be key in people vulnerable to stress. Since subjects who live with high levels of stress tend to consume more alcohol with the intention of reducing the anxiety that stress generates in their daily life. Therefore, we are interested in exploring whether a dysfunction in Ox1R signaling may be a risk factor that subsequently contributes to continuous and/or intermittent alcohol intake (Fig. 1b,c).

To do this, we block the activation of Orx1R with a specific antagonist (SB-334867, SB) in the NAc Shell. Our results showed that the SB antagonist reversed the effect of ethanol on anxiety levels in rats (Fig. 1b,c). Furthermore, we observed an up-regulation in Orx1R density and a tendency to increase orx-A concentration in response to acute ethanol administration (Fig. 1b,c). Both the increase in the number of receptors and levels of orx-A were enhanced in presence of the antagonist and ethanol in NAc (Fig. 1b,c) .

Our study was the first to show that a damage in Orx1R signaling can induce a certain tolerance to the anxiolytic effect of alcohol intake. Future studies are required to explorer whether impaired orexinergic transmission may subsequently lead to excessive and uncontrolled alcohol consumption.

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