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PERSPECTIVE

The multifaceted potential of the lipid transmitter oleoylethanolamide to treat alcohol-induced neuroinflammation and alcohol use disorders

Is there a need for new pharmacotherapies to treat alcohol use disorders (AUDs)? AUD is a highly prevalent condition in the world population that causes medical, psychological, personal, social and economic problems. The most severe dimension of AUDs is alcohol dependence, a condition in which individuals lose control over alcohol intake despite the negative consequences. Although some medications have been approved for this purpose, existing pharmacotherapies are not effective for all people due to the heterogeneity of AUDs. Current approved medications include: Disulfiram (Antabuse®), which induces an aversion to drink by increasing alcohol metabolism-derived acetaldehyde; Naltrexone (ReVia®, Vivitrol®), a competitive opioid antagonist for μ-receptors that decreases heavy drinking and prevents relapse; Acamprosate (Campral®), an indirect partial agonist at N-methyl-D-aspartic acid glutamate receptors and antagonist at metabotropic glutamate receptors that is used to prevent relapse in detoxified alcoholics. Strong efforts to develop new medication are ongoing, with multiple pharmacological targets being explored. Whereas initial medical development for AUDs focused on the binge/intoxicating state of addiction, current challenges involve finding new targets for the craving and withdrawal/negative emotional states of addictive behaviour. Thus, extensive research is currently looking for new drugs that correct the dysfunction of the reward and stress systems by improving the motivational signs of withdrawal, which are a hallmark of alcohol dependence. Some new targets, such as γ-aminobutyric acid or glucocorticoid receptors, have shown their efficacy not only in preclinical models but also in human laboratory models (Gabapentin and Mifeprestone, respectively) (Koob and Mason, 2016).

Alcohol consumption, apart from addiction, leads to neuroinflammation, which, when long-lasting, contributes to brain damage and cognitive decline and is a common phenomenon in several neuropsychiatric disorders that co-exist with AUDs, such as depression. Certain patterns of alcohol consumption are especially harmful, such as binge heavy alcohol drinking, which is common among some alcoholics and frequently occurs among young drinkers. Binge drinking is a risk factor for developing an alcohol dependence, especially when bingeing occurs during adolescence. This frequent pattern of alcohol intake is known to cause neuroinflammation that contributes to the neurotoxic effects of the drug and it can also influence alcohol drinking and behavioural patterns (reviewed in Montesinos et al., 2016). However, prevention of neuroinflammation is a largely overlooked aspect in the search for new pharmacotherapies for AUDs. In this perspective, it is argued that alcohol-induced neuroinflammation is an important process to take into account in the development of medication for AUDs and provide preclinical scientific evidence for a drug candidate that ameliorates both alcohol-induced neuroinflammation and several aspects of AUDs.

Oleoylethanolamide (OEA) as a candidate for treating alcohol-induced neuroinflammation/neurotoxicity and AUDs: During the last decades, emerging investigations have focused on the role of lipid transmitters, instead of traditional neurotransmitters, as targets for many neuropsychiatric disorders. Lipid transmitters are small molecules that are primarily generated enzymatically by the cleavage of phospholipids, which are structural components of the cell membrane. Among lipid transmitters, acylethanolamides such as OEA and palmitoylethanolamide have been shown to be upregulated in several brain disorders and to exert neuroprotective properties though the modulation of oxidative stress, neuroinflammation, glial cell proliferation or neurotransmission. The disorders in which these acylethanolamides participate include stroke, multiple sclerosis, Parkinson's disease, traumatic brain injury, Hungtington's disease, post-traumatic stress disorder, depression or substance use disorders, among others.

In this perspective, I focus on OEA, a lipid transmitter that targets peroxisome proliferator-activated receptor-α, a nuclear receptor that has been involved mainly in the regulation of energy homeostasis. One of the crucial milestones of OEA in counteracting alcohol effects is probably its potential to block alcohol-induced neuroinflammation and neurotoxicity. Neuroinflammation is a complex process involved in the physiophatology of AUDs and one exciting discovery about OEA lies in its properties to prevent the alcohol-induced innate immune over-response, showing potent anti-inflammatory, antioxidant and neuroprotective actions during alcohol binge intoxications in preclinical murine models. Specifically, OEA pretreatment is able to block the upregulation of toll-like receptors (TLR)-4 and subsequent pro-inflammatory mediators (citokines, chemokines, enzymes) and danger molecules (high mobility group box-1) that result from such activation, providing neuroprotection in the frontal cortex of rats exposed to alcohol (Antón et al., 2017). Preclinical models of alcohol binge drinking have, to some extent, shown translational evidence for the presence of an exacerbated inflammatory response in human binge drinkers, since the production machinery (mRNA) of TLR-4 and its related pro-inflammatory mediators were found to be high in regular young binge drinkers. This over-expression of inflammatory markers was associated with worse neuropsychological performance among female binge drinkers (Orio et al., 2018). Interestingly, several of these pro-inflammatory markers correlate with elevated endogenous levels of OEA in human binge drinkers. This endogenous release of OEA is probably an attempt by the organism to counteract alcohol-induced toxic effects to maintain homeostasis (Antón et al., 2018b).

Additionally, the anti-inflammatory properties of OEA exert antidepressant actions during alcohol withdrawal in rats (Antón et al., 2017), which undoubtedly could be a strategy to prevent relapse, due to the close relationship between emotional negative states and AUDs in humans. Indeed, OEA may contribute to the therapeutic effects of antidepressants since elevated plasma OEA levels have been found in depressed patients treated with antidepressants (Romero-Sanchiz et al., 2019), suggesting that it could be useful to treat the emotional negative states associated with AUDs.

Interestingly, the beneficial properties of OEA to counteract alcohol responses extend to some AUD-related behaviours in preclinical murine models. Thus, OEA prevents alcohol self-administration and cue-induced alcohol-relapse, ameliorates alcohol-induced physical withdrawal effects (Bilbao et al., 2016) and modulates motivational behaviours (motivational withdrawal) that are important to prevent relapse, such as the hypohedonic-like emotional state and the depressive-like behaviour during abstinence (Sayd et al., 2015; Antón et al., 2017).

As happens in humans, rat plasma OEA levels are increased in response to alcohol, presumably as the aforementioned homeostatic response to counteract alcohol effects. Indeed, the elevations in plasma levels of OEA have been documented both in laboratory rats (Bilbao et al., 2016), in human binge drinkers (Antón et al., 2018b) and in AUD-diagnosed patients (Garcia-Marchena et al., 2017). Interestingly, OEA levels persist as long as alcohol is present in the rats' blood, decreasing gradually during withdrawal (Bilbao et al., 2016) and this advances the duration of abstinence in humans (Garcia-Marchena et al., 2017), strengthening the homeostatic hypothesis of OEA in the organism.

OEA mechanisms to counteract alcohol responses and remaining questions:

Central versus peripheral responses: Both central and peripheral mechanisms have been described for OEA actions. On the one hand, OEA is mobilized in the rat nucleus accumbens and cerebellum after intraperitoneal alcohol administration (Bilbao et al., 2016) and it can be generated in the brain by acetylcholine and glutamate receptor activation, which are also altered by alcohol. Additionally, it has been demonstrated that OEA rapidly crosses the blood-brain barrier (Plaza-Zabala et al., 2010). The anti-inflammatory and neuroprotective actions of OEA in the brain are related to its strong ability to counteract alcohol-induced oxidative stress, by inhibition of the canonical pro-inflammatory TLR-4/NF-kB pathway, reducing lipid peroxidation, apoptotic mechanisms and accumulation of toxic products, such as high mobility group box-1 in the frontal cortex (Antón et al., 2017).

On the other hand, OEA was discovered as a satiety factor released by the intestine in response to high caloric food and the small intestine is precisely one the first tissues, together with the brain nucleus accumbens, of OEA mobilization after alcohol exposure (Bilbao et al., 2016). Endogenous OEA production in the small intestine could be the consequence of alcohol-induced sympathetic activity. Recently, a new mechanism has been discovered, centred on the intestine, for the

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protective actions of OEA against alcohol-induced inflammation. It has been shown that alcohol binges disrupt the rats' intestinal barrier allowing the entry of bacteria from the intestinal lumen into the mesenteric lymph nodes and bacterial products, such as endotoxins, into the circulation. This bacterial translocation is a potent cause of immune activation and peripheral inflammation induced by alcohol. Pretreatment with OEA during alcohol binges prevents inflammation and immune activation in the gut and preserves the structure of intestinal tight junction proteins altered by alcohol, which indicates that OEA pretreatment protects the integrity of the intestinal barrier damaged by alcohol. As a consequence, the entry of bacteria and/or bacterial products is prevented, reducing the strong immune activation and peripheral inflammation caused by alcohol, with consequences in cortical neuroinflammation (Antón et al., 2017, 2018a). Interestingly, the effects of OEA in reducing alcohol self-administration and cue-induced reinstatement appear to be dependent on the integrity of the peripheral sensory system, since the deafferentiation of the small intestine abrogates OEA effects (Bilbao et al., 2016).

Hypothalamic-pituitary-adrenal axis activation versus blood-brain barrier disruption: Immune system activation may promote neuroinflammation through different pathways. The sympathetic activity of peripheral pro-inflammatory cytokines activates the hypothalamic-pituitary-adrenal axis by vagus nerve afferent stimulation and transmits cytokine signals to the brain, and it has been proven that OEA drastically reduces alcohol-induced gut inflammation and HPA axis activation (Sayd et al., 2015; Antón et al., 2017, 2018a). The effect of OEA in the modulation of the HPA stress axis (reduction of alcohol-induced increase in corticosterone, Antón et el., 2017) is an outstanding finding, taking into account that dysregulation of the HPA axis is a relevant factor to explain the neurobiology of addiction. Whereas alcohol intoxication activates the HPA axis, chronic alcohol use disrupts it, contributing to a reward function deficit, anhedonia and craving, which plays a role in compulsive alcohol intake. OEA actions in the HPA axis and blocking neuroinflammation appears to contribute to the amelioration of motivational withdrawal. The anti-anhedonic and anti-depressant actions of OEA would contribute to the improvement of motivational withdrawal and prevention of relapse. However, the potential role of OEA in treating compulsive alcohol drinking remains to be tested in more sophisticated animal models, such as alcohol vapour chamber models, and in human laboratory experiments.

Additionally, peripheral cytokines can reach the brain by the circumventricular organs through blood-brain barrier saturable cytokine transporter mechanisms, or they may access the brain by alcohol-induced blood-brain barrier dysfunction. Whether OEA protects from a blood-brain barrier dysregulation in vulnerable brain areas affected by alcohol remains to be elucidated.

Contribution of the microbiome-gut-brain axis to neuroinflammation: The intestine has been identified as a central organ for directing the actions of OEA, including the previously mentioned actions in vagal afferents and the intestinal barrier structure. Given the importance that the gut-brain communication is acquiring in recent years to explain CNS functioning, mention should be made of the gut mechanisms that mediate OEA protective functions in alcohol-induced neuroinflammation. In this sense, the microbiome has been pointed out as a novel relevant factor to explain aspects of cognition, emotion and behaviour. Recent studies indicate that OEA is able to modulate gut microbiota composition in mice under physiological conditions, influencing gut-specific immune responses (Di Paola et al., 2018). However, the possible effects of OEA in regulating the gut microbiota composition altered by alcohol and its consequences in immune and inflammatory responses are still unknown.

Conclusion: An examination has been made of the scientific evidence of the capacity of the lipid transmitter OEA to prevent alcohol-induced neuroinflammation and neurotoxicity, and its potential to treat AUDs. Whatever the mechanisms involved, recent evidence indicates that OEA has beneficial properties to counteract many responses related to alcohol consumption, such as prevention of alcohol-induced neuroinflammation and brain damage, limiting alcohol intake, amelioration of physical and motivational withdrawal effects and prevention of relapse in preclinical animal models.

The implication of neuroinflammation in the origin or maintenance of the addictive behaviour is currently the focus of intense research since it remains controversial. Future research will discern whether these two important consequences of alcohol intake are interrelated. So far, preclinical studies in laboratory animals have identified possible neuroinflammatory targets such as TLR-4, activated microglia, ciclooxygenase-2 or the monocyte chemoattractant protein-1 for treating AUDs by modulating the immune system (reviewed in Montesinos et al., 2016). The strong anti-inflammatory and antioxidant actions of OEA by TLR-4 inhibition point to this biolipid as a good candidate in this regard. Finally, due to the nature of the compound, an oleic acid derivative, OEA-based nutraceuticals could emerge as a future co-adjuvant therapy to prevent alcohol-induced neuroinflammation /neurotoxiciy, and to treat AUDs.

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