Neuropharmacology 122 (2017) 148–160

Contents lists available at ScienceDirect

Neuropharmacology

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

Invited review

A role for the peripheral immune system in the development of alcohol use disorders?

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ARTICLE INFO

Article history:
Received 31 October 2016
Received in revised form
6 April 2017
Accepted 7 April 2017
Available online 9 April 2017

Keywords:
Alcohol use disorders
Microbiota
Leaky-gut
Lipopolysaccharides
Peptidoglycans
Cytokines
Gut-barrier function
Probiotics
Prebiotics

ABSTRACT

Preclinical studies have largely supported that alcohol-consumption induces the development of an important neuro-inflammation and this neuro-inflammation contributes to alcohol-drinking behaviors, notably through TLR4 and LPS related mechanisms. The neuro-inflammation originates from a direct interaction of ethanol with the neuronal and immune brain cells, but also from the generation of an inflammation at the periphery. Ethanol in particular interacts with the intestine to develop a gut dysbiosis and an increase in gut permeability, that allows the liberation of bacterial fragments to the systemic circulation and induces a pro-inflammatory response in the systemic circulation and peripheral organs, and in particular the liver. Peripheral cytokines or activated peripheral cells may cross the blood-brain barrier and activate neuro-inflammation. In humans, peripheral inflammation and intestinal dysbiosis are related to symptoms of alcohol use disorders (AUD), such as depression, anxiety and alcohol-craving, However, the dysbiosis, could also participate in a different manner to the symptomatology of the addiction, possibly by interacting with the stress system, by interfering with the sleep processes and altering the abilities for social interactions. The role of the gut suggests that interventions with probiotics or prebiotics might in the future be of interest for the treatment of the addiction.

This article is part of the Special Issue entitled “Alcoholism”.

Contents

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http://dx.doi.org/10.1016/j.neuropharm.2017.04.013
0028-3908/

1. Introduction

Excessive alcohol consumption is known for several decades to strongly stimulate the innate immune system and to play a major role in the development of alcoholic liver disease (Szabo et al., 2011). Recent observations of neurons using immune signaling as a way to communicate (Boulanger et al., 2001), of the role of immune signaling for cognition (Williamson and Bilbo, 2013) but also that LPS elicited immune activation of the microglia leads to neurodegeneration (Lehnardt et al., 2003) support a role for the immunity in brain physiology and physiopathology. In the case of AUD, a large literature arising from animal and human studies have suggested a role for neuro-inflammation in the pathophysiology of the disease (Robinson et al., 2014). However, important questions remain as to the origins of the neuro-inflammation. In this article we will discuss the possibility that at least a part of the inflammation arises from peripheral origins and in particular from the gut, giving arguments for potent interventions targeting peripheral sources to decrease the neuro-inflammation and possibly the addiction. Several points will be evoked successively in the manuscript. We will start by describing the importance of neuro-inflammation for psychopathology and the development of AUD, where part of the neuro-inflammation is likely related to a direct effect of ethanol at the brain level. We will then examine the role of peripheral sources of inflammation in the development of AUD, and focus on the role of the gut, the disruption of the gut barrier and the development of gut dysbiosis in AUD. Other potent sources of inflammation like the gut wall, the liver and the adipose tissue will also be suggested. We will then describe how systemic inflammation and gut barrier are related to the expression of AUD in humans and animals. The mechanisms whereby changes in the gut microbiota may be related to the development of AUD will be evoked and in particular the role of stress, social impairments and sleep disturbances. Finally, we will suggest that the intestine might serve as a new target for pharmacological or nutritional interventions for the treatment of AUD.

2. Importance of neuro-inflammation in psychopathology and for the development of AUD

2.1. The sickness behavior and the role of low grade, peripheral inflammation

The sickness behavior theory (Dantzer and Kelley, 2007) supports that during infections, bacteria or viruses activate the immune system leading to the production of pro-inflammatory cytokines, which reach the brain and induce a sickness reaction characterized by behavioral symptoms such as fatigue, lassitude, inability to concentrate, irritability, loss of appetite and withdrawal from social interactions (Dantzer et al., 2008; Konsman et al., 2002). These symptoms are close to the symptoms of depression, but also to other psychopathological conditions including AUD (Cordovil De Sousa Uva et al., 2010; Schuckit, 1994), and when the inflammation persists, the symptoms may become more pronounced and chronic, and the condition developed by the individual, fulfill the criteria of a mental disorders, like for instance a major depression disorder (Dantzer et al., 2008; Smith, 1991; Yirmiya, 1996; Yirmiya et al., 1999). A score of experimental and clinical arguments supports the role of inflammation in the development psychiatric disorders. Increasing pro-inflammatory cytokines in healthy volunteers by the intravenous injection of LPS (Krabbe et al., 2005; Reichenberg et al., 2001) or treating cancer or hepatitis C patients with IFN-α or IL-2 leads to the development of various psychiatric symptoms (Capuron et al., 2001, 2000; Musselman et al., 2001). In major depression, a subgroup of individuals that present with a high baseline plasma level of pro-inflammatory cytokines are improved by medications targeting the immune system (Raison et al., 2013). Finally, altering the immune system of rodents during gestation may induce the development of autism spectrum or schizophrenia-related behavior in the off-springs (Bauman et al., 2014; Hsiao and Patterson, 2011).

2.2. Existence of a neuro-inflammation in AUDs

Several studies over the past few years have supported both the existence of a neuro-inflammation in AUD, but also that it plays a causal role for its development. Binge intoxication induces an inflammatory response in the brain of rats (Crews et al., 2006)) or mice ((Crews et al., 2013, Kane et al., 2014), as does a chronic exposure to ethanol of mice (Whitman et al., 2013, Lippai et al., 2013). This observation is not limited to rodents, as neuro-inflammation is also observed port-mortem in AUD individuals (Crews et al., 2013, Vetreno et al., 2013, He and Crews, 2008). Data from studies using microarray analyses of brain genes also support the role of neuro-inflammation in AUD. Several immune genes are overexpressed in the brain of strains of mice selected to present an alcohol-preference (Saba et al., 2006, Mulligan et al., 2006), and this effect was not related to ethanol administration, consistent with a role of neuro-inflammation in the predisposition to drinking. In addition, exposure of mice to ethanol vapors induce important changes in the expression of immune related genes in astrocytes, microglial, and neuronal cells of the amygdala, the nucleus accumbens and the prefrontal cortex (Osterndorff-Kahanek et al., 2015), suggesting also that ethanol works as an immunomodulator. However, multiple processes could be involved in the development of a neuro-inflammation after exposure to ethanol.