Pharmacology & Therapeutics 144 (2014) 321–337

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

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

Associate editor: I. Kimura

Role of microglia in ethanol-induced neurodegenerative disease: Pathological and behavioral dysfunction at different developmental stages

Jing-Yu Yang [a], Xue Xue [b], Hua Tian [a,c], Xiao-Xiao Wang [a], Ying-Xu Dong [a], Fang Wang [a], Ya-Nan Zhao [a], Xue-Chun Yao [a], Wei Cui [a], Chun-Fu Wu [a,*]

[a] Department of Pharmacology, Shenyang Pharmaceutical University, Shenyang 110016, PR China
[b] State Key Laboratory of Biomacromolecules, Insititute of Biophysics, Chinese Academy of Sciences, Beijing 100101, PR China
[c] Department of Pharmacology, Qiqihar Medical University, Qiqihar 161006, PR China

ARTICLE INFO

Available online 10 July 2014

Keywords:
Alcohol
Microglia
Neuroinflammation
Behavior
Neurodegeneration
Animal models

ABSTRACT

Alcohol abuse can result in significant alterations to the structure of the brain and ultimately to behavioral dysfunctions. Epidemiological studies have shown that alcoholism is closely associated with impaired memory and judgment. However, the degree of deficit (brain injury) depends on factors such as the age of onset, duration of heavy drinking, continuous versus periodic (binge) drinking and the typical amount consumed per session. In recent years, neuroinflammation has been proposed as one of the alcoholism-induced neuropathological mechanisms, since increased levels of microglial markers are observed in the brains of both post-mortem human alcoholics and various alcohol-treated animals, from newborn or adolescent rodents to adult rodents. Many studies have investigated how microglia modulate alcohol-induced behavioral changes such as cognitive deficits, abnormal locomotor activity, motor impairment and mood disturbance. Importantly, we try to characterize and compare the distinct features in different ethanol (EtOH)-induced neurodegenerative disease (NDD) models. Moreover, mounting evidence indicates that in response to certain environmental toxins, microglia can become over-activated under oxidative stress, releasing pro-inflammatory mediators that cause central nervous system (CNS) disease. The molecular mechanisms involve free radical formation and the release of pro-inflammatory cytokines that are detrimental to neighboring neurons and interfere with the molecules regulating cell–cell interactions. The identification and understanding of the cellular and molecular mechanisms of microglial activation are described, as well as multiple downstream targets, in different alcohol-treated animal models. This review might contribute to the development of treatments and/or therapeutic agents that can reduce or eliminate the deleterious effects of alcohol-induced NDD.

Contents

Abbreviations: A(1)R, adenosine A(1) receptor; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; AP-1, activator protein-1; AQP4, aquaporin-4; ARG1, arginase 1; Aβ, β-amyloid; BDNF, brain derived neurotrophic factor; BHT, butylated hydroxytoluene; C3G, anthocyanin cyanidin-3-glucoside; CCL, Chemokine (C–C motif) ligand; CNS, central nervous system; dbcAMP, dibutyryl-cAMP; EtOH, ethanol; FASD, fetal alcohol spectrum disorder; GFAP, Glial fibrillary acidic protein; GSH, glutathione; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; LXR, liver X receptor; MAPK, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein-1; MWM, Morris water maze; NDD, neurodegenerative disease; NF-κB, nuclear factor-kappa B; NO, nitric oxide; NOX, NADPH oxidase; PAMPs, pathogen-associated molecular patterns; PD, Parkinson's disease; poly I:C, polyinosine–polycytidylic acid; PRRs, pathogen recognition receptors; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; TLR, toll-like receptor; TNF, tumor necrosis factor; TRIF, toll/IL-1 receptor domain-containing adaptor-inducing interferon.

* Corresponding author at: Department of Pharmacology, Shenyang Pharmaceutical University, Box 31, 103 Wenhua Road, 110016 Shenyang, PR China. Tel./fax: +86 024 23843567.
E-mail address: wucf@syphu.edu.cn (C.-F. Wu).

http://dx.doi.org/10.1016/j.pharmthera.2014.07.002
0163-7258/

1. Introduction

Microglia, the resident immunocompetent and phagocytic cells of the central nervous system (CNS), comprise approximately 10% of adult brain cells (Kraft & Harry, 2011). Microglial activation is a graded process which provides a very early and rapid response to various immunologic stimuli and injuries in the brain. Physical microglial activation often results in secretion of neurotrophic factors that limit tissue injury by aiding in repair processes. However, abnormally activated microglia secrete a variety of pro-inflammatory mediators such as cytokines, chemokines and reactive oxygen species (ROS) that are known to potentiate the inflammatory cascade and to cause neuronal damage by enhancing oxidative stress and activating cell-death pathways. Thus excessive and protracted microglial reaction can become deleterious and lead to chronic neuronal inflammation and degeneration (Felderhoff-Mueser et al., 2005). On the other hand, these features of microglia offer opportunities to find potential targets for the diagnosis and therapy of the early stage of neurodegenerative disease (NDD), which is closely associated with inflammation and degeneration of neurons.

An important role of microglia in alcohol-induced brain damage has been suggested since the 1990s. In recent years, it has become evident that microglia are heavily involved in ethanol (EtOH)-induced NDD. Studies have shown that glial cells are even more sensitive to EtOH-induced degeneration than neurons in the brain (Korbo, 1999; Santos et al., 2013). Increased levels of microglial markers are linked to EtOH-induced neuroinflammation at such a high frequency that this has been recognized as one of the features of EtOH-induced neuropathology (He & Crews, 2008). However, in preclinical and clinical studies, it is not possible to control for the duration or amount of alcohol administration and the age at which such exposure occurs in human beings. Therefore, animal models provide a framework for the integration of these variables. The gene sequences of rats, mice, and other mammals are similar to those of humans, and the modeling method is relatively simple and easy to carry out (Muller & Hein, 2010). In recent studies, animal models of EtOH-induced neurodegeneration are classified by the age of the animals or the duration of the drinking period. The detailed behavioral characterization of these models allows us to study the neurochemical and molecular mechanisms of alcoholism. On the other hand, alcohol may have specific effects depending on differences in dosage, duration, pattern, or period of EtOH exposure. Not surprisingly, the response of microglia, as a pathological symptom of the early stage of EtOH-induced NDD, occurs via different mechanisms in different animal models. Thus, it is necessary to acquire a clearer picture to understand the role of microglia in EtOH-induced degeneration of neurons. This review includes an overview of previous studies on the action of microglia that relate to EtOH-induced brain damage, and summarizes current evidence which provides new insights into the underlying mechanisms of alcohol-related NDD. Various therapeutic strategies for modulating the response of microglia are evaluated, as well as the current developmental state of agents that protect against EtOH-induced neurotoxicity.

2. Models of ethanol-induced injury

2.1. Ethanol and central nervous system damage

2.1.1. The risk of alcohol abuse

Currently there is an upward trend in the consumption of alcoholic beverages in most countries. Most people enjoy drinking alcohol to attenuate negative (e.g., anxiety, tension, stress) and enhance positive (e.g., relaxation, elation) affective states (Cooper et al., 1995; Kassel et al., 2000; Levenson et al., 1980; Sayette, 1999). Physicians can use the available research evidence describing the known benefits and risks associated with alcohol consumption when counseling their patients regarding alcohol-related decisions and behaviors (Doll, 1998; Standridge et al., 2004). The benefits of light-to-moderate alcohol consumption include lower risk for dementia (Letenneur, 2004; Ruitenberg et al., 2002), lower rates of myocardial infarction, heart failure, or coronary and cerebrovascular disease (Abramson et al., 2001; Ashley, 1982; Cooper et al., 2000; Mukamal et al., 2003; Solomon et al., 2000), reduced risk of ischemic stroke (Mukamal et al., 2005; Patra et al., 2010; Sacco et al., 1999), and decreased risk of diabetes (Wannamethee et al., 2002). Other data have defined the metabolic and biochemical influences of alcohol that, in turn, explain the mechanisms by which mild-to-moderate alcohol consumption improves these health outcomes. However, excessive levels of binge drinking lead to the development of tolerance and dependence. This further promotes excessive consumption, which is associated with alterations in the physiology, structure and functions of multiple organs such as liver, stomach, brain, kidney and lung, and may even cause cancer. Noticeably, alcoholics are much more susceptible to nervous system diseases and their average life span may be shorter than normal people (Harper & Matsumoto, 2005).

2.1.2. The genetic factors involved in alcohol abuse

Alcohol abuse is associated with a wide range of physical, mental and social factors (Kohnke, 2008). The initiation of alcohol intake is powerfully influenced by environmental factors; however, genetic factors are emerging as increasingly important in affecting regular patterns of alcohol abuse, based on plentiful data (Buscemi & Turchi, 2011; Kimura & Higuchi, 2011; Pan et al., 2013) from family, twin and adoption studies. Furthermore, susceptibility and vulnerability to alcohol abuse are determined by a complex array of genetic factors, which account for 50–60% of the liability (Mayfield et al., 2008). Genetic variants, especially single nucleotide polymorphisms (SNPs), can result in different endophenotypes that are potential contributors toward alcohol abuse. SNPs affect several alcohol-metabolizing enzymes, particularly alcohol dehydrogenases (ADHs) and aldehyde dehydrogenases (ALDHs). The SNPs in and around the ADH4 and ALDH1A1 genes are significantly associated with alcoholism susceptibility (Liu et al., 2011). The potential relevance of SNPs to the risk of alcohol abuse has also been discussed in several studies (Dick et al., 2006; Edenberg et al., 2006; Franke et al., 2000). For instance, a SNP in the GABA(A) alpha 2 receptor subunit gene (GABRA2) has different effects on alcohol dependence across different developmental stages. This SNP is associated with alcohol dependence throughout adulthood, but not during childhood or adolescence. SNPs in the cannabinoid receptor 1 gene (CNR1), on the other hand, are associated with attenuated negative responses to alcohol (Marcos et al., 2012). In addition, another study found that SNPs in the μ-opioid receptor (OPRM1) gene moderate the hedonic effects of alcohol in heavy drinkers, indicating that these variants contribute to mood modulation (Ray et al., 2013). Together, these studies will help in understanding the role of genetic variants in processes such as ethanol metabolism, motivational behavior and reward responses, which may affect the risk of alcohol abuse.

2.1.3. The symptoms of alcohol abuse

Acute alcoholism occurs after a single episode of heavy drinking. According to the toxic symptoms, acute alcoholism is divided into three periods — excitement, ataxia and lethargy — but the boundary between these stages is indefinite. When acute alcohol intoxication occurs,