Ageing Research Reviews 42 (2018) 28–39

Contents lists available at ScienceDirect

Ageing Research Reviews

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

Review

Role of microglia-neuron interactions in diabetic encephalopathy

Yuan Liu[a,b,1], Mingchao Li[a,b,1], Zuo Zhang[a], Yun Ye[a,*], Jiyin Zhou[b,**]

[a] Department of Pharmacy, Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan 646000, China
[b] National Drug Clinical Trial Institution, The Second Affiliated Hospital, Army Medical University, Chongqing, 400037, China

ARTICLE INFO

Keywords:
Diabetic encephalopathy
Microglia
Neuron
Interaction
Signaling pathway

ABSTRACT

In the central nervous system, the primary immune cells, the microglia, prevent pathogenic invasion as the first line of defense. Microglial energy consumption is dependent on their degree of activity. Microglia express transporters for the three primary energy substrates (glucose, fatty acids, glutamine) and regulate diabetic encephalopathy via microglia-neuron interactions. Microglia may play a sentry role for rapid protection or even ablation of impaired neurons. Neurons exhibit hyperactivity in response to hyperglycemia, hyperlipidemia, and neurotoxic factors and release potential microglial activators. Microglial activation is also regulated by proinflammatory factors, caspase-3 activity, $P2X_7$ receptor, interferon regulatory factor-8, and glucocorticoids. Modulation of microglia in diabetic encephalopathy may involve CX3CL1, p38 MAPK, purinergic, and CD200/CD200R signaling pathways, and pattern recognition receptors. The microglia-neuron interactions play an important role in diabetic encephalopathy, and modulation of microglial activation may be a therapeutic target for diabetic encephalopathy.

1. Introduction

The duration of diabetes increases the prevalence of diabetic neuropathy, which is delayed during the stabilization of blood sugar (Pop-Busui et al., 2017). Diabetic patients with a diagnosis of less than 12 months have 10% diabetic neuropathy, which increases to as high as 50% at 25 years after diagnosis (Guastella and Mick, 2009). The most frequent symptoms of diabetic neuropathy are paresthesia, numbness, and burning (Schemmel et al., 2010). One possible mechanism for diabetic neuropathy is persistent inflammation caused by the secretion of a large number of proinflammatory factors and pro-oxidative substances (Pabreja et al., 2011). Importantly and in contrast to classical neurotransmitters, the proinflammatory factors are dominantly expressed by glia (non-neurons), including microglia, astrocytes, and oligodendroglia in the brain (Marchand et al., 2005; Tsuda et al., 2005). Immune surveillance is the most common function linked to microglia in both healthy and diseased states. Microglia continuously survey their microenvironment by extending and retracting their highly motile processes (Davalos et al., 2005; Nimmerjahn et al., 2005). This property is crucial to elicit prompt responses to infection or injury. Microdamage in the brain such as microaneurism or the incipient demise of one single neuron can be detected and repairs initiated without triggering a more substantial activated state (Giaume et al., 2007; Hanisch and Kettenmann, 2007; Hughes, 2012).

Glial cells significantly outnumber neurons in the central nervous system (CNS). Microglia have a different morphology from other glial cells and neurons and make up approximately 5% to 12% of the total cells in the CNS (Polazzi and Monti, 2010). As the main immune cells in the CNS, microglia function as resident macrophage-like cells. As the first line of defense to prevent pathogenic invasion, microglia recognize, sequester, and process antigens to generate innate immune responses (Fu et al., 2014; Gosselin et al., 2010). Microglia possess several diverse roles in both physiological and pathological procedures, such as the regulation of inflammation and/or the immune response (Lampron et al., 2013), identification of pathogens/bound antibodies, antigen presentation, cytotoxicity (Boche et al., 2013; Kaur et al., 2013), and phagocytosis (Fu et al., 2014; Kettenmann et al., 2011).

Microglia act as neuroprotectors in numerous ways, including the clearance of aberrant neurons, tissue debris, and synapses (Boche et al., 2013; Kettenmann et al., 2011), stripping of synapses, promotion of neurogenesis, and suppression of destructive inflammation through the excretion of anti-inflammatory factors such as transforming growth

* Corresponding author at: Department of Pharmacy, Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan 646000, China. Tel.: +86-830-3165787; fax: +86-830-3165787.
** Corresponding author at: National Drug Clinical Trial Institution, the Second Affiliated Hospital, Army Medical University, Chongqing, 400037, China. Tel.: +86-23-68755311; fax: +86-23-68755311.
E-mail addresses: yeyunluzhou@foxmail.com (Y. Ye), zhoujiyin@gmail.com (J. Zhou).
[1] Equal contributors.

https://doi.org/10.1016/j.arr.2017.12.005
Received 14 August 2017; Received in revised form 7 November 2017; Accepted 8 December 2017
Available online 13 December 2017

factor-β and interleukin-10 (IL-10) (Chen and Trapp, 2016). Microglial activation has been implicated in some neurodegenerative illnesses. Increased microglial activation in old diabetic rat brains was demonstrated by a markedly elevated average microglia volume (Hussain et al., 2014). Diabetic patients have higher microglial proliferation in both the non-lesional hemisphere and the peri-infarct region of acute cerebral infarction, and they display neuronophagia in the peri-infarct region (Li et al., 2011). APP/PS1xdb/db mice show significant increases in microglial activation (Ramos-Rodriguez et al., 2015). An enriched environment promotes cognitive comorbidities of type 1 diabetes, possibly by partially suppressing microglial activation in the dentate gyrus of the hippocampus in diabetic rats (Piazza et al., 2014). Exercise protects diabetic (ZDF) rats with more inactive microglia owing to the reduced cytoplasm with extremely ramified processes and smaller amounts of tumor necrosis factor (TNF)-α, IL-6, and IL-1β in the hippocampus (Yoo et al., 2015). Whether microglial activation is a cause or an effect of diabetes-related neurodegeneration or whether microglial activity indeed inhibits neurodegeneration is a heavily researched subject.

In diabetic encephalopathy, microglia participating in the inflammatory process do not occur in isolation but are likely affected by neurons and neighboring cells including astrocytes, infiltrating circulating immune cells (like macrophages), and the blood-brain barrier. An understanding of the role of microglia-neuron interactions in diabetic encephalopathy is indispensable to comprehend the inflammatory components during disease progression. Thereby, it has currently become a pressing matter to better confirm the mechanisms of microglia-neuron interactions to develop more efficacious therapeutic drugs to manage and treat diabetic encephalopathy. This paper reviews the microglial status, phenotypes, origination, interaction between neurons, and molecular and signaling pathways of microglia in diabetic encephalopathy.

2. Microglial status, phenotypes, and origination

Ramified microglia (resting form) and amoeboid microglia (activated form) are the two main morphological states (Boche et al., 2013; Tsuda et al., 2005). Microglial proliferation is infrequently detected and considered to be “quiescent” under normal conditions. Ramified microglia consist of a relatively inactive status with ample thin and ramified processes and a small soma. In contrast, under physiological conditions, microglia actively sense their microenvironment with their thin and ramified processes (Nimmerjahn et al., 2005). Ramified microglia express receptors of proinflammatory factors and play an immune role to maintain CNS homeostasis (Gosselin et al., 2010).

Unlike ramified microglia, amoeboid microglia (the macrophage-like cells) have fewer but thicker processes and larger cell bodies (Kettenmann et al., 2011). The amoeboid state is usually linked to microglial activation in response to CNS injuries, including hyperglycemia, infection, autoimmune inflammation, or neuronal injury. When activated by infection, inflammation, or trauma, microglia experience many stereotypic alterations in morphology, number, function, and mRNA expression. Briefly, the microglial soma increases in volume, and their long, thin ramifications retreat until the microglia acquire an amoeboid shape with few ramifications (Tsuda et al., 2005). Inflammation stimulates microglia to move, proliferate, and synthesize/release proinflammatory factors that can activate neighbor neurons, microglia, and astrocytes. The released proinflammatory factors also upregulate complement receptor 3 (Eriksson et al., 1993), cluster differentiation 14 (CD14), and toll-like receptor 4 (TLR4) (Tanga et al., 2004). Microglia display a M1 activation state marked by IL-1β, IL-6, IL-12, tumor necrosis factor-α (TNF-α), CD16, CD86, and Fc receptor 16 and a M2 activation state marked by arginase 1, chitinase-3-like protein, found in inflammatory zone 1, CD206, IL-4, and IL-10 (Benson et al., 2015). The M1 activation state is considered to represent proinflammatory activation, and the M2 activation state constitutes anti-inflammatory and neuroprotective activation (Amantea et al., 2015; Kaur et al., 2013; Lampron et al., 2013; Taylor and Sansing, 2013). This classification is the same as that of macrophages (Boche et al., 2013). Microglia are significantly different from macrophages with distinctive molecular markers for differentiation (Diaz-Araya et al., 1995; Gautier et al., 2012).

Graded morphological changes in microglia help to differentiate highly ramified or surveillant microglia from amoeboid or activated ones. Microglia possess an amoeboid morphology during regular CNS development and are converted to a ramified form after they mature (Boya et al., 1979). The aging microglia are converted from an extremely ramified morphology to less ingenious arbors. The mosaic distribution of aging microglia becomes more irregular and show increased numbers (Wong, 2013). Aging microglia also display a slower and less dynamic response to tissue damage (Hefendehl et al., 2014). In addition, microglia possess other morphological states, including multinucleated and rod-shaped microglia (Boche et al., 2013). However, the microglial morphology is not affected by the release of proinflammatory factors stimulated by low doses of systemic lipopolysaccharide (Sierra et al., 2007). Hence, microglial responses are regulated by an arsenal of signaling pathways that result in an effector phenotype related to neurotoxicity or neuroprotection. Dysregulated microglial responses may be due to a triggering receptor or the loss of a constitutive inhibitory signal (Hanisch, 2002).

Microglia originate from cells that infiltrate the brain during late embryonic and postnatal life (Alliot et al., 1999; Butovsky et al., 2014; Chan et al., 2007; Ginhoux and Prinz, 2015; Kettenmann et al., 2013; Kierdorf et al., 2013; Milligan and Watkins, 2009). Microglia progenitors can be recognized in the yolk sac even before the emergence of hematopoietic cells (Alliot et al., 1999). Microglial progenitors infiltrate the brain via formation of the blood circulation during fetal development and finally contribute to the microglial pool (Hanisch and Kettenmann, 2007). After birth, the replenished microglial pool depends on the self-proliferation of embryonic invaded/resident microglia, without irradiation or bone marrow transplantation (Ajami et al., 2007; Bruttger et al., 2015). Resident microglia quickly proliferate after activation (Romero-Sandoval et al., 2008) and are unrelated to the timing of microgliosis. In contrast, bone marrow-derived hematopoietic stem cells constantly renew the perivascular microglia (Hickey and Kimura, 1988), particularly during CNS inflammation (Lassmann et al., 1993). Under physiological conditions, the functions of perivascular and resident microglia are similar. Resident microglia tend to polarize toward the M1 phenotype, which is proinflammatory and neurotoxic, whereas perivascular microglia mainly polarize toward the neuroprotective M2 phenotype during retinal degeneration (Jin et al., 2017). In contrast to the anti-inflammatory effect of perivascular microglia, resident microglia trigger both proinflammatory and anti-inflammatory effects (Romero-Sandoval et al., 2008). The major proinflammatory receptors are expressed in both perivascular and resident microglia (Pocock and Kettenmann, 2007).

Perivascular microglia, together with endothelial cells, pericytes and astrocytes, form the functional blood-brain barrier. Perivascular microglia are antigen-presenting cells that function in bidirectional and permanent immunological monitoring of endothelial cells and their perivascular localization (Hickey and Kimura, 1988), which enables them to survey the influx of blood-borne components into the CNS (Dudvarski Stankovic et al., 2016). In soon after reperfusion of transient middle cerebral artery occlusion mice, microglia became activated in the stroke penumbra and start to extend cellular protrusions towards adjacent blood vessels. All microglia in the penumbra are related to blood vessels within 24 h post reperfusion and partially fully engulf them. In the same time frame, blood vessels became permissive for blood serum components. Blood serum proteins (fibrinogen) that into the tissue provides molecular cues leading to the recruitment of microglia to blood vessels and to their activation in vitro. Subsequently, these perivascular microglia started to consume endothelial cells by