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Interaction between astrocytic colony stimulating factor and its receptor on microglia mediates central sensitization and behavioral hypersensitivity in chronic post ischemic pain model

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ABSTRACT

Accumulation of microglia occurs in the dorsal horn in the rodent model of chronic post ischemic pain (CPIP), while the mechanism how microglia affects the development of persistent pain largely remains unknown. Here, using a rodent model of CPIP induced by ischemia–reperfusion (IR) injury in the hind-paw, we observed that microglial accumulation occurred in the ipsilateral dorsal horn after ischemia 3h, and in ipsilateral and contralateral dorsal horn in the rats with ischemia 6h. The accumulated microglia released BDNF, increased neuronal excitability in dorsal horn, and produced pain behaviors in the modeled rodents. We also found significantly increased signaling mediated by astrocytic colony-stimulating factor-1 (CSF1) and microglial CSF1 receptor (CSF1R) in dorsal horn in the ischemia 6h modeled rats. While exogenous M-CSF induced microglial activation and proliferation, BDNF production, neuronal hyperactivity in dorsal horn and behavioral hypersensitivity in the naïve rats, inhibition of astrocytic CSF1/microglial CSF1R signaling by fluorocitric or PLX3397 significantly suppressed microglial activation and proliferation, BDNF upregulation, and neuronal activity in dorsal horn, as well as the mechanical allodynia and thermal hyperalgesia, in the rats with ischemia 6h. Collectively, these results demonstrated that glial CSF1/CSF1R pathway mediated the microglial activation and proliferation, which facilitated the nociceptive output and contributed to the chronic pain induced by IR injury.

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Limb ischemia-reperfusion (IR) injury is a common but serious clinical syndrome occuring after crush injury or traumatic occlusion of the peripheral arteries. Limb IR, while potentially impairing the function of remote organs including acute respiratory distress syndorm (Takhtfooladi et al., 2016) and cognitive deficiency (Chen et al., 2012), produces the persistent pain syndrome, the chronic post ischemic pain (CPIP) (Coderre et al., 2004). Recent studies demonstrated that the hind limb IR activated pain related signaling pathways in the spinal cord (Choi et al., 2015; Ji et al., 2009), and spinal cord stimulation therapy greatly relieved the syndrome of CPIP (Naoum and Arbid, 2013). These suggested the critical involvement of neuroadaptation in spinal cord in the development of CPIP. We previously reported the extensive activation of microglia in spinal dorsal horn in CPIP animal model (Xu et al., 2016). Increasing evidences suggested the critical role of spinal microglia in the induction of central neuroinflammation and sensory sensitization in the setting of neuropathic pain (Milligan and Watkins, 2009; Watkins et al., 2007). However, the actual role of spinal glia in the development of CPIP remains unknown.

Remarkable accumulation of microglia has been observed in the injuried brain area (Hanisch and Kettenmann, 2007) and in dorsal horn of neuropathic pain models (Calvo and Bennett, 2012). Abundant evidences suggested that the activated microglia released numerous proinflammatory cytokines and chemokines, which eventually increased the neuronal excitability and led to the central sensitization in neuropathic pain (Kawasaki et al., 2008; Zhao et al., 2017). Brain-derived neurotrophic factor (BDNF), derived from spinal microglia, served as a final common path in convergence of

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noxious stimulation *via* increasing synaptic drive to excitatory neurons whilst reducing that to inhibitory neurons (Coull et al., 2005; Trang et al., 2011; Biggs et al., 2010). Glutamatergic transmission, as the primary excitatory neurotransmission in nociceptive pathways in dorsal horn, relayed the peripheral nociptive information into the pertinent supraspinal regions, and the enhanced glutamatergic synaptic transmissions in dorsal horn contributed to the induction of mechanical allodynia and thermal hyperalgesia in the condition of chronic pain (Kuner, 2015; Luo et al., 2014). Previous studies found that BDNF may enhance the expression (Caldeira et al., 2007) and activity (Nakazawa et al., 2001) of NMDA receptor subunit NR2B, and increase the expression and synaptic insertion of AMPA receptor subunit GluR1 in central neurons (Caldeira et al., 2007; Wu et al., 2016). Currently, whether BDNF derived from microglia contributes to the central sensitization and behavior hypersensitivity remains unknown in the rodent model of CPIP.

The accumulated microglia may come from diverse origins, including the infiltration of peripheral macrophages (Ulvestad et al., 1994; Brockhaus et al., 1996), the resident microglial chemotactic migration (Calvo and Bennett, 2012) and the resident microglial progenitor self-renewal (Calvo and Bennett, 2012; Denes et al., 2007; Wirenfeldt et al., 2007; Ajami et al., 2011), while little is known about the origins of the accumulated microglia in dorsal horn in the neuropathic pain model. A recent study reported that peripheral nerve injury increased the production and releases of colony-stimulating factor-1 (CSF1) from primary sensory neurons, which subsequently regulated the microglial proliferation in dorsal horn (Guan et al., 2016). Interaction between CSF1 and its receptor CSF1R (Yu et al., 2008) substantially regulated the proliferation, differentiation, and survival of myeloid lineage cells (Yu et al., 2008; Lee et al., 1993; Patel and Player, 2009; Chitu et al., 2016). Gene knockout or pharmacological inhibition of CSF1R leads to a significant loss of microglia in the embryo and mature CNS (Elmore et al., 2014; Erblich et al., 2011; Ginhoux et al., 2010; Stanley et al., 1983). Similarly, deficiency of CSF1 leads to the abnormal brain development and function (Michaelson et al., 1996). The expression of CSF1 and CSF1R were upregulated in the neuroinflammatory diseases, including Alzheimer's disease (Lue et al., 2001; Gowing et al., 2009), amyotrophic lateral sclerosis (Akiyama et al., 1994); injuried brain (Raivich et al., 1998); brain tumors (Bender et al., 2010), HIV-associated cognitive impairment (Lentz et al., 2010). Our previous study also found that prolonged peripheral limb ischemia (5 h) increased the expression of CSF1 and CSF1R in dorsal horn (Liao et al., 2016). Based on these previous findings, in the present study, we aimed to further study the effect of different duration of ischemia (3 or 6 h) on the celluar and behavioral adaptation, and the role of CSF1/CSF1R signaling to bridge the crosstalk between astrocyte and microglia in doral horn, as well as its functional significance in central sensitization and behavioral hypersensitivity in the rodent model of CPIP.

Here, using a CPIP model, we found that limb IR induced significant microglial activation and proliferation in the dorsal horn, which was mediated by the interaction between astrocytic CSF1 and microglial CSF1R. The activated microglia increased the synthesis and secretion of BDNF, and subsequently enhanced neuronal activity and glutamatergic transmission in dorsal horn, thus contributing to the behavioral hypersensitivity in the rodent model of CPIP.

2. Materials and methods

2.1. Animals and CPIP model

All experimental procedures were approved by the Institutional Animal Care and Use Committee at Shichuan University, and were performed in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. Adult male Sprague-Dawley rats weighing 300-350g were purchased from Chengdu Dashuo Biological Technology Co., Ltd., one of the certified suppliers of experimental animals for Shichuan University. Animals were housed in the Institutional Biological Rodent Unit on a 12-h light/dark cycle at a room temperature of 22 ± 1 °C with free access to food and water. Limb ischemia was established with an O-ring with 7/32 in. internal diameter tightly passed around the left hindlimb just proximal to the ankle joint as previously described (Coderre et al., 2004). O-ring was then cut off 3h or 6h later for reperfusion. Sham rats had the ankle surrounded with the same O-ring which was cut and did not occlude blood flow to the hindpaw.

2.2. Intrathecal catheter implantation

As previously described (Wu et al., 2004), the rats were anesthetized with pentobarbital (50 mg/kg), and a PE-10 tube (BD, USA) was implanted into the lumbar enlargement (L4) through intervertebral L5-6 space and dura. The catheter was then tunneled under the skin and 2 cm of the free end was fixed at the neck. The catheter placement was verified by observing transient limb paralysis induced by injection of 2% lidocaine (10 μL). Only those rats showing complete paralysis of both hind limbs and the tail after the administration of lidocaine were used for the subsequent experiments. The intrathecal (i.t.) catheter implantation was performed 2 days before the baseline behavioral tests. The position of the PE tubing at the lumbar enlargement was visually verified by exposing the lumbar spinal cord at the end of experiment.

2.3. Drugs and administration

All the following drugs were administrated after limb IR. PLX3397 (Selleck Chemicals, U.S, No. S7818) was either dissolved in 0.5% HPMC/1% Tween 80/2.5% DMSO and intragastric (i.g.) administrated at dose of 30mg/kg a day as previous reported (Thompson et al., 2015), or mixed into a standard 50g/kg standard rodent diet (chow) at a dose of 50 mg/kg body weight a day based on references manufacturer recommend (Elmore et al., 2014; DeNardo et al., 2011; Sluijter et al., 2014). The rodent chow mixed with PLX3397 was measured every day. PLX3397 was administrated for consecutive 7 days. Minocycline (Hovione Ltd, Loures, Portugal, No. 10118-90-8) 100 μg/10 μl was administrated through the catheter inserted into subarachnoid space (i.t.) for consecutive 7 days. 1 nmol/L of fluorocitrate was prepared as following: 4 mg of fluorocitric acid barium salt (FC) (Sigma, U.S, No. F9634) was first dissolved in a mixed solution of 0.5 ml of hydrochloric acid (1 N), one drop of Na_2SO_4 (0.1 M) and 1 ml of phosphate buffer (0.1 M). The solution was centrifuged at 12,000g for 5 min, and the supernatant was then withdrawn and diluted with 4.8ml saline solution. A bolus of 10 μL FC was intrathecally administrated for consecutive 3 days. The M-CSF (Sigma, U.S, No. SRP3332) 2 μg was intrathecally administrated for consecutive 3 days. The injection of experimental drugs was completed at least 1 h before behavioral tests.

2.4. Behavioral tests

Animals were habituated to the test environment daily for 2 days before the baseline test. Behavioral tests including withdrawal responses to mechanical and thermal stimuli were carried out in a quiet testing room by an investigator who was unaware of the group. Each treatment group used for the behavioral tests consisted of 10 rats. To evaluate the behavioral response to mechanical stimulation, we determined the 50% paw-withdrawal threshold (PWT) as previously described (Xu et al., 2016;

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