Neuroimmune factors alter neuronal function:

The ability of neuroimmune factors to act as modulators/ regulators of neuronal physiology was revealed in early physiological experiments involving electrical recordings of neuronal activity or imaging of intracellular Ca\(^{2+}\) levels from live cells in vivo or in vitro. For example, our studies of cultured hippocampal or cerebellar neurons demonstrated that acute exposure to the chemokines CCL2 or CXCL10 altered basic neuronal properties such as resting intracellular Ca\(^{2+}\) levels, Ca\(^{-}\) signaling evoked by activation of metabotropic glutamate receptors (mGlur), and action potential generation (Nelson and Gruol, 2004; van Gassen et al., 2005). Ca\(^{-}\) is an important second messenger that controls numerous neuronal functions, action potential generation and responses to transmitters are essential for synaptic transmission, which mediates brain function and, consequently, behavior. In contrast, acute exposure to the cytokine IL-6 did produce changes in intracellular Ca\(^{2+}\) or electrical activity of cultured hippocampal or cerebellar neurons. However, chronic treatment with IL-6 increased resting Ca\(^{2+}\) levels, enhanced the Ca\(^{-}\) response evoked by activation of mGlur, and depressed action potential generation in the cultured neurons (Nelson et al., 2002, 2004). Thus, both chemokines and cytokines can alter important neuronal properties, and often the same properties, although the conditions for these actions (e.g., acute vs. chronic exposure) and likely the behavior consequences differ.

Studies of transgenic mice that chronically express elevated brain levels of CCL2 (CCL2-tg) or IL-6 (IL-6-tg) further demonstrated that these neuroimmune factors can alter neuronal and synaptic function under conditions of long-term exposure, such as occurs in neurodegenerative and psychiatric disorders or chronic brain infection (Gruol, 2013, 2015). In both transgenic lines, genetic manipulation targeted the increased expression to astrocytes, which are closely associated within the brain and are regulators of synaptic function. These studies were carried out in CCL2-tg mice with chronic hyperalgesia from the IL-6 tg or CCL2-tg mice at the excitatory glutamatergic Schaffer collateral (SC) to CA1 pyramidal neuron (SC-CA1) synapse, the most highly studied synapses in the brain (Figure 1A).

Synaptic responses were recorded extracellularly (field potential recordings) and were evoked by brief electrical stimulation of the SC. Results showed that excitatory synaptic responses at the SC-CA1 synapse evoked by SC stimulation were enhanced in hippocampus from IL-6-tg mice (Nelson et al., 2012), whereas excitatory synaptic responses at the SC-CA1 synapse evoked by SC stimulation were not altered in hippocampus from CCL2-tg mice (Bray et al., 2013). However, in hippocampus from CCL2-tg mice an enhancement of synaptic plasticity further demonstrated that these neuroimmune factors were involved in the expression of increased excitability of the pyramidal neurons (Bray et al., 2013).

Neuroimmune factors alter synaptic plasticity:

Emerging research also indicates that neuroimmune factors can modulate synaptic plasticity, a fundamental brain process that is altered during the development of memory and learning. Synaptic plasticity is a short- or long-term change in the efficacy of synaptic transmission induced by repetitive activity of synaptic networks. Both presynaptic and postsynaptic synaptic changes are involved in synaptic plasticity. Experimentally, synaptic plasticity is induced at the SC-CA1 synapse by high-frequency electrical stimulation (HFS) of the SCs. Two types of synaptic plasticity are produced, a short-term (sec-min) enhancement of synaptic responses termed post-tetanic potentiation (PTP) followed by a long-term (hours to days or longer) enhancement of synaptic responses termed long-term potentiation (LTP). Both forms of synaptic plasticity play a role in memory and learning. Synaptic plasticity (PTP and LTP) induced by HFS was not altered by the elevated levels of IL-6 or CCL2 in hippocampal slices from the IL-6-tg and CCL2-tg mice, respectively. In contrast, studies in hippocampal slices from wildtype rats showed that acute application of IL-6 produced a depression of PTP and LTP at the SC-CA1 synapse (Tancredi et al., 2000). Building on this work are studies showing that HFS results in IL-6 production by glial cells and serves as a negative regulator of LTP. IL-6 can alter another form of synaptic plasticity termed long-term synaptic depression (LTD). IL-6 reduces presynaptic glutamate release (e.g., CCL2) and in behavioral studies, that IL-6 is involved in cognitive function (Gruol, 2015).

Interactions with alcohol:

Although synaptic plasticity was not altered in hippocampus from the IL-6-tg and CCL2-tg mice, our recent studies on the effects of alcohol (ethanol) revealed that covert neuroadaptive changes had been produced by chronic exposure to IL-6 or CCL2. Alcohol/neuroimmune interactions were of interest because alcohol significantly alters brain function, transiently or persistently depending on the pattern of use, recent studies indicate that alcohol (and other drugs of abuse) can induce glial cells to produce elevated levels of neuroimmune factors in the brain (Lacagnina et al., 2017), and alcohol use disorders are often co-morbid with other detrimental conditions associated with elevated levels of neuroimmune factors in the brain (e.g., major depression). Using the IL-6 tg and CCL2-tg mice to model long-term exposure of the brain to these neuroimmune factors, we have examined the possibility that IL-6 or CCL2 can produce neuroadaptive changes that alter the effects of alcohol, an interaction that could play a role in the development of alcohol dependence.

In the absence of alcohol, LTP and PTP in hippocampus from IL-6-tg, CCL2-tg and their respective control mice (Wildtype (WT)) were not altered. Exposure to pharmacologically relevant doses of alcohol, 20 mM (considered a moderate dose)
and 60 mM (considered a high dose), produced a dose-dependent depression of both LTP and PTP in hippocampus from control mice. However, in hippocampus from IL-6 tg mice acute exposure to 20 mM or 60 mM alcohol had no apparent effect on LTP or PTP, whereas in hippocampus from CCL2-tg mice, 20 mM acute alcohol enhanced PTP and LTP while 60 mM had no apparent effect. Thus, alcohol revealed covert neuroadaptive changes produced by the neuroimmune factors that alter learning on cellular processes involved in memory and learning. Consistent with this effect, in a behavioral test of learning, cued and contextual fear conditioning, acute alcohol depressed cued and contextual learning in control mice but not in CCL2 mice (Bray et al., 2013). The contextual conditioning task in this test is considered to be hippocampal-dependent, whereas the cued conditioning task is thought to be hippocampal-independent. These interactions between IL-6 or CCL2 and alcohol suggest that there are common synaptic targets between these neuroimmune factors and alcohol.

The mechanisms mediating the covert neuroadaptive effects of IL-6 and CCL2 and interactions with alcohol have yet to be identified. However, our recent studies point to the involvement of presynaptic mechanisms that regulate transmitter release (Gruol et al., 2020). In these studies, synaptic responses elicited during HFS showed an initial facilitation followed by a depression, a pattern of changes known to be dependent on presynaptic mechanisms underlying transmitter release. The facilitated synaptic responses were of similar magnitude in hippocampus from IL-6 tg and control mice (Figure 1B1). Acute alcohol exposure (60 mM) significantly enhanced the facilitated synaptic responses in the hippocampus from the IL-6tg mice with no effect on the facilitatory synaptic responses in hippocampus from the control mice (Figure 1B2). Regression analysis showed that in the presence of alcohol, the magnitude of the facilitatory synaptic responses in the hippocampus from the IL-6tg mice predicted the magnitude of LTP at a 27% level, whereas without alcohol the predicted value was only 15%. In control mice, in the presence of alcohol the magnitude of the facilitatory synaptic response predicted the magnitude of LTP at a 3% level, whereas without alcohol the predicted value was 30%. These results are consistent with neuroadaptive effects of IL-6 on presynaptic machinery involved in transmitter release. Studies by others have shown that alcohol alters presynaptic mechanisms of transmitter release, resulting in decreased release (Gioia and McCool, 2017). Thus, the lack of effect of alcohol on LTP in the IL-6tg mice may result from IL-6-induced neuroadaptive effects that blocked the ability of alcohol to reduce transmitter release. Consistent with this possibility, synaptic responses elicited by single SC stimulations were also increased by alcohol exposure in the hippocampus of the IL-6tg mice.

Taken together, these studies provide representative examples of how individual neuroimmune factors can affect neuronal processes that underlie brain function. Identification of the cellular targets and neuronal consequences of neuroimmune actions is basic to an understanding of the role of the neuroimmune system in the brain. This area is understudied, critical to an understanding of the mechanisms underlying the effects of the neuroimmune system on cognitive function, and ripe for investigation.

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