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Neuropharmacology

Neuroimmunology and synaptic function

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This Special Issue of Neuropharmacology is devoted to specific aspects of neuroimmunology and synaptic function. It contains 12 invited reviews from eminent scientists from all around the globe. These distinguished experts in the field of neuroimmunology and neuroscience provide exciting reviews on a range of topics, which include pro-inflammatory cytokines, cannabinoids, obesity, and neurodegenerative diseases. These articles demonstrate that there is a diverse impact of the immune system in synaptic function. Whilst it has been many years since it was first recognized that the immune and central nervous system communicate, it has only been in the last 20 years or so that detailed knowledge has begun to appear about this interaction. Neurons and glia and indeed other cell types are involved in many neuro-modulatory cross talk mechanisms. For example cytokines can modulate both directly and indirectly neuronal activity in both the central and peripheral nervous systems. We also now know that cells in the large and small intestine can directly communicate with many peripheral and central neurons and glial cells. Indeed research into how immune molecules modulate synaptic function could be considered a relatively new field of scientific investigation.

In the first of these reviews [Jones and Lynch \(2005\)](#) look at the factors that shift microglia from resting states to non-resting states and the markers of this activation. They show elegantly how microglia can adopt different phenotypes in response to different internal and external stimuli. For example acute activation (M1 activation state) may be protective while chronic activation of microglia is damaging to

tissue. They also discuss the relationship between microglial activation, aging and decreased synaptic plasticity. The review also discusses how astrocyte activation may impact on long-term potentiation, an important model for memory. Finally they outline evidence investigating a link between microglial activation, elevated levels of A-beta and decreases in synaptic signaling particular through the use of transgenic models of Alzheimer's disease. Aging is also a subject matter in the review by [Patterson \(2015\)](#). Here she shows that aging may sensitize the response of microglia to signals triggered by an immune challenge. Patterson discusses this and the release of agents such as IL-1 β in aging and the effect this may have on cognitive processes including synaptic plasticity particularly in the hippocampus, an area involved in many memory mechanisms. She also discusses the role of BDNF and how it may be disrupted during excessive production of IL-1 β by microglia in aging. [Delpeche et al., \(2015\)](#) also set out their review to look at specific aspects of microglia in neuronal plasticity. They discuss the consequences of acute and chronic stress on microglia dependent behavioral and plastic changes. Indeed these changes cause very robust activation of microglia in many brain regions including the pre frontal cortex and hippocampus. They suggest that altered neuron-microglia crosstalk may be the cause of this stress induced microglial activation. To follow on from these three reviews, [Norden et al. \(2015\)](#) discuss the topic of priming of microglia in the aging brain and in addition its role in traumatic brain injury and neurodegenerative diseases. In this review they discuss

microglia as mainly pro-inflammatory although go on to show evidence that they can act as anti-inflammatory agents. For example a down regulation of the fractalkine receptor on microglia in aged mice with prolonged activation showed depression-like behaviors and prolonged social withdrawal. All of these studies show that acute and transient increases in neuro-inflammation can lead to cognitive impairments in healthy mice whilst similar immune challenges can lead to amplified and exaggerated cognitive impairments in conditions where microglia are primed.

[Gruol \(2015\)](#) reviews the specific role of the pro-inflammatory cytokine, IL-6 in synaptic function. Like other immune factors IL-6 is also produced by astrocytes, microglia and in certain conditioned neurons. Growing evidence now shows that IL-6 is expressed at increased levels during altered cognitive function and behavior. She also goes on to look at some of the clinical evidence to support this. The review also discusses the evidence that both acute and chronic IL-6 has direct neuronal and synaptic actions. In one transgenic model she shows that the cerebellum has the highest level of IL-6 expression in GFAP-IL-6 mice and interestingly they also have the most pathology. She also provides very convincing evidence that IL-6 plays an important role in synaptic plasticity at least in the hippocampus. [Kwilasz et al \(2015\)](#) concentrated their review on the signaling pathways and function of another pro-inflammatory cytokine, IL-10 (also expressed by microglia astrocytes and neurons) and include its role in some neuroimmune diseases such as multiple sclerosis, neuropathic pain and Parkinson's disease. They also outline some of the IL-10 based therapies used to treat some of these immune diseases. For example in animal models of Parkinson's disease, IL-10 therapies may reduce dopaminergic cell damage and the related microglial activation.

The effects of immune molecules on synaptic excitability has been of interest for a number of years now. Specifically the effect of pro-inflammatory cytokines such as IL-1 β , TNF- α and IL-6 on neuronal excitability is reviewed by [Vezzani &](#)

[Viviani \(2015\)](#), and especially those effects on ion channel activity and synaptic function. They provide an overview of the effects of IL-1 β , TNF- α and IL-6 on voltage gated Na⁺, Ca⁺⁺ and K⁺ channels in the peripheral and central nervous system. Pre- and post-synaptic effects of IL-1 β and TNF- α are also discussed. Finally the long-term effects of these molecules on seizure susceptibility and cognition is presented.

Immunosuppressive therapy has significantly grown over the last number of years not just post transplantation surgery but in patients with autoimmune disease such as rheumatoid arthritis or ankylosing spondylitis. However the neuropsychological disturbances caused by such acute and chronic treatment is not yet fully understood. [Bosche et al., \(2015\)](#) review the main mechanisms of action and therapeutic use of small molecule-drugs (e.g. cyclosporine, tacrolimus and mTOR inhibitors) and the effects they have on neuropsychological functions. It will be interesting to note in the future if neuropsychological therapy will also be required in some instances with immune suppression. On the other hand it is suggested that immunomodulation may improve cognitive function. This is a question addressed by the review of [Zheng et al. \(2015\)](#). The authors outline the brain-periphery interaction pathways and cognitive regulation that may be occurring and they include endocrine and metabolic signaling here. They allude to the ever interesting field of the brain-gut-microbiota axis and its modulation of cognition in diseases such as stroke, Alzheimer's, Huntington's disease, and traumatic brain injury.

[Rossi et al \(2015\)](#) overview the effects of inflammatory cytokines and endocannabinoids in the regulation of synaptic transmission. On the one hand they look at the neuroprotective action of the endocannabinoid system by inhibiting inflammatory-dependent synaptic alterations, and on the other hand how the control of synaptic transmission by endocannabinoids is altered by pro-inflammatory cytokines such as IL-1 β and TNF- α . In the review they also discuss the role of endocannabinoids and inflammatory cytokines in emotional disorders. For

example they show the evidence of an interaction between IL-1 β , CB $_1$ R s and anxiety disorders. [Speio et al \(2015\)](#) review the interesting field of synaptic elimination following central and peripheral neuronal injury and in particular spinal motor neuron input changes as a result of proximal lesions. It is now known that active microglia and astrocytes may remove synapses from injured motor neurons at least during the first stages of synaptic rearrangements. However immune molecules would seem to have dual roles in development and repair. However they suggest that not all synaptic plasticity within the spinal cord is beneficial. Central sensitization of pain pathways may develop in response to noxious stimuli.

This special edition on neuroimmunology and synaptic function finishes with a review on the effect of obesity, elevated circulating cytokines and psychiatric diseases ([Arguilar-Valles et al., 2015](#)). The authors overview the adokines which include many of the pro-inflammatory cytokines including IL-6 and TNF- α and the anti-inflammatory cytokines including IL-10 and IL-1ra and others such as leptin. They go on to suggest that leptin and others such as adiponectin and resistin have a role in the pathophysiology of psychiatric disorders such as major depression. However they also suggest that other studies show an antidepressant effect of leptins.

This is a very exciting time for the disciplines of neuroscience and immunology and especially for that of neuroimmunology. In the next 5 to 10 years it is likely that we will see an explosion in this new field of study and especially that field of neuroimmunology, which interacts with synaptic function. I hope you enjoy reading this Special edition.

References

- Arguilar-Valles, et al., 2015. Obesity, adipokines and neuroinflammation. *Neuropharmacology* 96, 124e134.
- Bosche, K., Weissenborn, K., Christians, U., Witzke, O., Engler, H., Schedlowski, M., Hadamitzky, M., 2015. Neurobehavioral consequences of small molecule-drug immunosuppression. *Neuropharmacology* 96, 83e93.
- Delpech, et al., 2015. Microglia in neuronal plasticity: influence of stress. *Neuropharmacology* 96, 19e28.
- Gruol, D.L., 2015. IL-6 regulation of synaptic function in the CNS. *Neuropharmacology* 96, 42e54.
- Jones, R.S., Lynch, M.A., 2015. How dependent is synaptic plasticity on microglial phenotype? *Neuropharmacology* 96, 3e10.
- Kwilasz, A.J., Grace, P.M., Serbedzija, P., Maier, S.F., Watkins, L.R., 2015. The therapeutic potential of interleukin-10 in neuroimmune diseases. *Neuropharmacology* 96, 55e69.
- Norden, D.M., Muccigrosso, M.M., Godbout, J.P., 2015. Microglial priming and enhanced reactivity to secondary insult in aging, and traumatic CNS injury, and neurodegenerative disease. *Neuropharmacology* 96, 29e41.
- Patterson, S., 2015. Immune dysregulation and cognitive vulnerability in the aging brain: interactions of microglia, IL-1b, BDNF and synaptic plasticity. *Neuropharmacology* 96, 11e18.
- Rossi, S., Motta, C., Musella, A., Centonze, D., 2015. The interplay between inflammatory cytokines and the endocannabinoid system in the regulation of synaptic transmission. *Neuropharmacology* 96, 105e112.
- Spejo, A.B., Oliveira, A.L., 2015. Synaptic rearrangement following axonal injury: old and new players. *Neuropharmacology* 96, 113e123.
- Vezzani, A., Viviani, B., 2015. Neuromodulatory properties of inflammatory cytokines and their impact on neuronal excitability. *Neuropharmacology* 96, 70e82.
- Zheng, X., Zhang, X., Kang, A., Ran, C., Wang, G., Hao, H., 2015. Thinking outside the brain for cognitive improvement: is peripheral immunomodulation on the way? *Neuropharmacology* 96, 94e104.