Facebook: Brock Post – Post 4 Cerebellum and Immunity
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Cerebellum and Immunity

As mentioned in last week’s post, the cerebellum has several roles within the neuraxis including sensory information integration, learning motoric movements, modifying movements, controlling mood, affect, emotion and regulating immune functions. Previously, we have discussed how depression can be linked to immune dysregulation, sugar dysregulation and lack of exercise. I mentioned last week that exercise will increase the frequency of firing of the cerebellum. I also mentioned that the cerebellum may play a role in higher cognitive functions such as mood, affect and cognition. This week I would like to bring some of those concepts together with a central focus on the cerebellum’s role in immune function and how it relates to mood and affect.

Remember, if a patient states that they are depressed, it is always important to ask yourself: what is causing the depression? As mentioned earlier, the literature shows that depression is a multimodal and very complex problem. The literature also shows that approximately 30-50% of patients that suffer from depression are not responsive to antidepressant management. It is difficult to pinpoint one specific causative factor when it comes to depression. So far we have discussed the following considerations: decreased activation of frontal lobes, decreased activation of the cerebellum, decrease exercise, immune system dysregulation, gut inflammation creating central consequences and sugar dysregulation causing central consequences.

As mentioned in my week 2 post, the hypothalamus plays a role in depression through the hypothalamic-pituitary-adrenal axis (HPA). The hypothalamus can also play a role in depression when looking at it’s communication with the cerebellum. We know that depression lives in the frontal lobe and the frontal lobe communicates with the cerebellum all the time. The cerebellum also communicates very frequently with the hypothalamus, an area that plays a significant role in immune regulation. The frontal lobe and hypothalamus also communicate all the time. So once again we have this cross-talk between the frontal lobes, cerebellum and hypothalamus. If one area is not working well, then it is quite possible that there will be break down, functional lesions or negative plasticity in these other areas as well.
In recent literature, it has been hypothesized that cerebellar immunomodulation exists and it may be mediated by the hypothalamus. Anatomically, there is no direct connection between the cerebellum and the immune system. There is, however, a direct projection from the cerebellum to the hypothalamus named the cerebellohypothalamic projections. If the hypothalamus is important in immune regulation, then this pathway may serve as an important mediator in modulating the immune system and the cerebellum has immunomodulatory properties, then the cerebellum may have an indirect effect on depression (by altering immune function).

Projections from the cerebellum to the hypothalamus come from the three nuclei I discussed last week: the fastigial nucleus in the most medial portion of the cerebellum, the interposed (composed of the globus and emobiliform) and the dentate (the most lateral nucleus). These projections travel through the superior cerebellar peduncle to different areas in the hypothalamus.
We hypothesized that cerebellar immunomodulation may be mediated by the hypothalamus, in view of an important status of the hypothalamus in immunomodulation [11–13]. In addition, the findings of direct neuronal projections from the cerebellum to the hypothalamus, termed as cerebellohypothalamic projections, also provide a crucial clue for our hypothesis. The direct cerebellohypothalamic projections arise from all three deep cerebellar nuclei, the fastigial nucleus, IN, and dentate nucleus, and terminate to hypothalamic extensive areas and nuclei, such as the lateral, posterior and dorsal hypothalamic areas, and the dorsomedial and paraventricular nuclei.

Although morphological and electrophysiological studies have revealed that cerebellar nuclei consist of diverse neuronal populations and that both glutamatergic and GABAergic neurons form projections and local connections [23–25], neurotransmitters used by the cerebellohypothalamic projections are not well identified. Recently, we reported traveling routes and terminating sites for neuronal projections from the cerebellar IN to the hypothalamus and indicated that the direct cerebellohypothalamic projections had GABAergic and glutamatergic fibers [26]. In the two groups of different projections, GABAergic cerebellohypothalamic projections have been shown to transmit cerebellar immunomodulation [26], but glutamatergic projections have not been known concerning their delivery of cerebellar immunomodulation information.

Since there is no direct structural connection between the cerebellum and immune system, the immunomodulation by the cerebellum must be mediated by other structures and mechanisms. We hypothesized that the hypothalamus is a critical mediator transmitting cerebellar immunomodulation. The hypothesis was presented on the basis of the evidence that the hypothalamus, a regulating center of autonomic nervous and endocrine systems, has been well established for its important status in immunomodulation [11–13], and that a direct cerebellohypothalamic projection is found [14, 15]. Our current study supports the hypothesis and proposes that through the direct cerebellohypothalamic projections, the cerebellum transmits its immunomodulating information to the hypothalamus, and subsequently, the
hypothalamus exerts its regulation of immune function via autonomic nervous and endocrine systems, which have direct contact with lymphocytes by neurotransmitters and hormones. Recently, we have indicated that cerebellohypothalamic GABAergic projections mediate cerebellar immunomodulation [26]. Here, we provide further evidence that cerebellohypothalamic glutamatergic projections also deliver cerebellar immunomodulation information.

Since the cerebellar nuclei are final output sites by which cerebellar regulatory information is exported, immune changes caused by damage to cerebellar nuclei represent a regulation of immune system by the cerebellum.

However, it still requires clarification whether the cerebellar IN-hypothalamic glutamatergic pathway is also involved in transmitting the modulation of specific immune responses to antigen challenge.