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COMMENTARY

Cannabinoids – Can What Hurts You Make You Stronger?

Commentary on the article by Alvarez *et al.* on page 653

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Recently, cannabinoids have been implicated in a variety of positive brain developmental processes but at the same time have been thought to be associated with deleterious effects after acute exogenous exposure. In humans, maternal use of *Cannibis sativa* (marijuana) during pregnancy is associated with cognitive deficits in the offspring (1). In animals, deficits in glutamatergic transmission, abnormal learning in adulthood, and apoptosis in developing brain have been described with exogenous exposure (2–4). Like many systems that have been implicated in this type of duality (glutamatergic systems, e.g.), these compounds may behave differently in physiologic and endogenously derived circumstances, but when administered exogenously during critical periods, may result in adverse effects.

The endocannabinoids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), are arachadonic acid derivatives that signal through Gi-protein coupled receptors, mainly CB1 and CB2. They are important modulators of a variety of CNS developmental functions including synaptic transmission, neurogenesis, migration and proliferation (5). Complex physiologic functions such as control of movement, appetite, thermoregulation, nociception, motivation and memory are assumed to be modulated by these compounds (6). The CB1 receptors are found on neurons and are responsible for the psychoactive properties attributed to these compounds while the CB2 receptors are found primarily on lymphoid cells but are also seen on brain endothelial cells and glia. Acting through the CB2 receptor, endocannabinoids may be immunomodulatory with effects both within and outside of the CNS (7).

The CB1 receptor is expressed in fetal and early postnatal brain but its expression changes and wanes over development of the organism (8). Importantly, the CB1 receptors are prominently located in the subventricular areas during early development and in fetal neurons that no longer express the receptors as they mature (9). CB1 receptors are found in white matter areas like the commissural fiber tracts and the corpus callosum, only to disappear in adulthood (8). This transient appearance of the receptor has led some to suggest that the cannabinoid receptors are involved in very specific developmental events. Interestingly, the psychoactive effects of cannabinoids do not seem to be prominent in the fetal and neonatal brain and this corresponds nicely with the lack of receptors in areas known to transmit these functions (prefrontal cortex, e.g.) (10).

CB2 receptors, first described in the immune system, have been identified on microglia, astrocytes and in subpopulations of neurons in the brainstem but not the cortex. There is induction of the receptor during inflammation. The location of the receptor in the brain suggests a role in repair, proliferation and survival of neural cells (11). It therefore seems likely that the duality or paradox associated with the endocannabinoids might be resolved at the level of receptor specificity and location, as well as inducibility in times of stress.

Literature is accumulating for non CB1 and non CB2 receptors in brain (*e.g.*, the GPR55 receptor) since some of the effects of the cannabinoid agonists cannot be blocked by the traditional receptor antagonists (12). The location and function of the various receptors may explain some of the paradoxes that exist regarding these compounds.

Therefore, studies proclaiming the dangers and benefits of the cannabinoids might be analyzed with this in mind, although the receptor subtype does not explain all of the differences. For example, delta 9 tetrahydrocannabinol, the principal psychoactive cannabinoid in *Cannabis sativa*, was shown to enhance apoptosis *in vivo* and *in vitro* in neonatal but not adult rat brain *via* activation of c-jun N-terminal kinase and caspase-3 (13). The same drug given to infant rats and mice systemically or the agonist WIN 55, 212-2 given alone or in combination with ethanol resulted in apoptotic neurodegeneration in young brains. The CB1 receptor antagonist SR141716A abolished the effect (3). However, the WIN 55, 212-2 agonist was shown to *reduce* brain injury in the Vannucci model of systemic hypoxia and focal ischemia in 7 d old rats (14). The CB1 antagonist reversed the protection. Interestingly, there were no benefits of

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Abbreviations: CBD, Cannabidiol; **CGRP,** calcitonin gene related product; **TRP,** transient receptor potential

the drug when measured at 24 h by MRI, but clearly less apoptosis at 7 d was seen suggesting that the vasogenic edema component of the injury was unaffected by the cannabinoid. The endocannabinoid, anandamide, provided dose-dependent protection against lesions in developing white matter and cortical plate induced by the AMPA agonist S-bromowillardiine. However, anandamide did not provide robust protection against the gray matter lesions seen with ibotenate injections in the developing brain. These effects were blocked by CB1 antagonism but not by CB2 antagonism. These investigators were unable to confirm expression of CB2 receptors in the neonatal rat brain (15).

Cannabidiol (CBD) is an interesting endocannabinoid that does not evoke the psychoactive properties of its cousin anandamide, nor does it act through CB1 receptors. It appears to have high affinity for the transient receptor potential (TRP) V2 receptor (TRPV2) and TRP channel of ankrin type 1 (TRPA1) (16). The latter is a vanilloid receptor-like member of the TRP superfamily of nonselective, ligand-gated cation channels implicated in thermal sensing. This receptor is present in the brain and when CBD binds to it, evokes the release of calcitonin gene related product (CGRP) in dorsal root ganglia (17). CGRP may protect the brain through its modulation of growth hormones like erythropoietin or BMP7 (18,19). However, CBD has been reported to reduce striatal atrophy caused by 3-nitroproprionic acid but the protective effects were not reversed by CB1, TRPV1 or A2A receptor antagonism (20).

In this issue of *Pediatric Research*, the same investigators, who reported the early benefits of WIN 55, 212-2 in the rat HI model, now show that cannabidiol protects the newborn piglet brain from global hypoxia ischemia in the short term by improving hemodynamic and metabolic function in the brain in the early hours after injury. CBD treated piglets had fewer seizures suggesting that the drug may also act as an anticonvulsant, although this effect may be due to the less severe injury seen in the treated piglets. Importantly, there was a return of aEEG amplitude to baseline in 6 of the 8 treated piglets. Early recovery of the aEEG in humans has been associated with improved outcome (21). CBD appeared to protect against early brain injury histologically, although at 6 h after the injury, it is unknown if this effect is sustainable or functionally significant. No side effects were seen with the drug, suggesting that this drug may be a nontoxic alternative to other drugs currently under investigation.

However, it is perhaps too soon to recommend a clinical trial with CBD until the pharmacology and disposition are better understood. In addition, it would be important to do longer term structural and functional studies, even with immature rodents in an effort to determine sustainability of the encouraging effect reported here. The endocannabinoids pose an interesting point for consideration. Is it that which hurts you can make you stronger, or that certain "hurts" are not clearly harmful (like accelerated apoptosis reported as in the Hansen study (3)). Only time will tell.

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