This Week in The Journal

Links between Socioeconomic Status and Brain Size

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(see pages 1365–1373)

Disparities in childhood socioeconomic status (SES) are associated with differences in mental and bodily health, cognitive ability, and academic achievement. Functional imaging studies have identified several brain areas that likely contribute to the cognitive functions that vary with SES, and structural imaging studies have suggested that some variation in cognitive ability is rooted in differences in the size of particular brain regions. For example, multiple studies have found correlations between childhood SES and the volume of prefrontal cortex and hippocampus, structures involved in executive function and memory.

McDermotta et al. extend previous work on the relationship between SES and brain structure by examining subcortical structures and cortical subregions, exploring how structural differences might relate to cognitive abilities, and examining the stability of differences over time. Using data from 623 children and young adults, many of whom were scanned multiple times, the authors found correlations between SES (derived from parental education and occupation scores) and total white and gray matter volume, cortical sheet volume, cortical surface area, and volumes of thalamus, hippocampus, striatum, amygdala, and pallidum. These associations were mostly stable with age, but the relationship between hippocampal volume and SES grew stronger over time.

Within the cortex, SES was correlated with surface area of lateral prefrontal, anterior cingulate, lateral temporal, and superior parietal lobules. A database of brain functions derived from meta-analyses suggested that these areas are involved primarily in sensorimotor function, language, memory, and emotional processing. IQ also varies with SES and the volume or surface area of multiple brain areas; mediation analysis suggested that the relationship between SES and IQ was partially attributable to variations in surface area of the middle temporal gyrus, supramarginal gyrus, and anterior cingulate cortex, and to a lesser

extent, to variation in the volume of subcortical structures.

These data suggest that the relationship between SES and cognitive function stems partly from interactions between SES and brain structure. The direction of causality remains unclear, however. Environmental factors correlated with SES—such as home environment, school quality, and nutrition—might influence brain structure and cognitive abilities, but heritable factors that shape brain structure and function might also influence SES. Further investigation of these relationships is necessary.

Increases in intraocular pressure reduce GABA (red) levels at synapses (marked by synaptophysin, green) in the retina, but levels are restored by treatment with a 5-HT1A agonist. Blue is Hoechst staining. See Zhou et al. for details.

5-HT1A Serotonin Receptors in Glaucoma

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(see pages 1484–1504)

Glaucoma is a leading cause of blindness worldwide. It is characterized by degeneration of optic nerve fibers, often accompanied by an increase in intraocular pressure. Although increased intraocular pressure might produce mechanical stress on retinal ganglion cell (RGC) axons, the pathophysiological mechanisms linking intraocular pressure to axonal degeneration

remain poorly understood. Moreover, decreasing intraocular pressure does not always halt nerve degeneration. Elucidating the cellular and molecular factors leading to axonal degeneration might lead to the development of additional treatments to promote axon survival.

One factor hypothesized to contribute to RGC death in glaucoma is excitotoxicity. Such toxicity might be countered by enhancing inhibitory input from amacrine cells to RGCs. Zhou et al. show that this can be achieved by activating 5-HT1A serotonin receptors (5-HT1ARs). When intraocular pressure was increased in rats by cauterizing episcleral veins, retinal levels of 5-HT1ARs—which were highly expressed in the ganglion cell layer—decreased. The frequency of miniature IPSCs was lower in RGCs of glaucomatous retinas than in controls, but phosphorylation of protein kinase A (PKA) was increased. These effects were reversed by activating 5HT1ARs, which are $G_{i/o}$ -coupled receptors that inhibit cAMP production and thus reduce PKA activity. The 5-HT1AR agonist also increased the amplitude and frequency of miniature and spontaneous IPSCs in RGCs of control retinas, and this effect was countered by a cAMP analog. Most importantly, the 5-HT1AR agonist increased the density of RGCs remaining in retinas 4 weeks after intraocular pressure was increased. This effect was prevented by treating retinas with GABA_A receptor antagonist.

These results suggest that a PKA-dependent signaling pathway suppresses inhibitory input to RGCs and that this pathway is inhibited by activation of 5-HT1ARs. Because increasing intraocular pressure reduces 5-HT1AR expression, it increases PKA-dependent suppression of inhibition. This might contribute to excitotoxicity in RGCs. To test this hypothesis, future work should determine which cells express 5-HT1ARs and how PKA regulates GABA release from amacrine cells. Other cellular mechanisms through which 5-HT1AR agonists might increase RGC survival should also be investigated. But regardless of mechanism, 5-HT1AR agonists might slow vision loss in people with glaucoma.

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