Cocaine: Neuronal, Vascular and Glial Effect

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Glia, in particular astrocytes, are involved in neurovascular coupling "NVC" (a process of modulating cerebral hemodynamics in response to changes in neuronal activity), which can be disrupted by drugs (e.g., alcohol, cocaine) and diseases (e.g., Alzheimer's disease, addiction). The ability to distinguish neuronal from vascular effects remains a challenge, partially due to the technical limitations of current neuroimaging techniques to differentiate vascular from neuronal and astrocytic effects at sufficiently high spatiotemporal resolutions. To tackle this problem, we developed a multimodality optical imaging platform that enables simultaneous imaging of functional changes in hemodynamics (including cerebral blood flow - CBF, and hemoglobin oxygenation and deoxygenation) and intracellular calcium fluorescence (i.e., Ca^{2+}_i as a marker of neuronal or astrocytic activity), which allowed us to monitor the changes in the neurovasculature, tissue oxygen metabolism and large-scale neuronal/astrocytic activity at high spatiotemporal resolution over a large field of view *in vivo*. By combining genetically-encoded Ca^{2+}_i indicator (GCaMP6f) and transgenic animal model, we were able to quantitatively image large-scale CBF networks along with neuronal and astrocytic Ca^{2+}_i signaling. This allowed us to investigate the role of astrocytes in regulating vascular networks during stimulation (e.g., electrical sensory stimulation) and during rest. We showed that astrocytic Ca^{2+}_i signaling was associated with vasoconstriction following the stimulation-induced CBF increases, which suggests that astrocyte resets the neurovascular network. This is in contrast to neuronal Ca^{2+}_i signaling which was associated with vasodilation following sensory stimulation. Studies to assess cocaine's effects revealed that it decreased CBF and disrupted the neuronal and astrocytic Ca^{2+}_i transients in response to sensory stimulation, providing evidence of NVC uncoupling during cocaine intoxication. Additionally, these results demonstrate the capability of this imaging technique to investigate the consequences of drugs on astrocytes, neurons and neurovascular networks.