We have reported a synapse-specific mechanism of glucocorticoid regulation of hypothalamic magnocellular neurons. Thus, glucocorticoid-induced retrograde endocannabinoid (eCB) actions are spatially restricted to glutamate synapses, and do not spill over onto neighboring GABA synapses, despite the expression of functional CB1 receptors at GABA synapses. The functional restriction of eCBs to glutamate synapses may be the result of extracellular buffering of the messengers by astrocytes. We tested this by recording whole-cell synaptic currents in hypothalamic slices following manipulations to reduce glial buffering mechanisms, including dehydration-induced glial retraction and blocking glial metabolism with fluorocitrate. Under these conditions of attenuated glial function, glucocorticoids elicited an eCB suppression of both glutamate and GABA release, suggesting spillover of eCBs onto GABA synapses. In the dehydration model, the glucocorticoid-induced suppression of GABA release, but not glutamate release, was prevented when extracellular viscosity was increased and diffusion retarded with the large neutral molecule dextran. These results suggest that restriction of the actions of glucocorticoid-induced endocannabinoids to glutamate synapses is controlled by astrocytes, and that attenuation of glial buffering leads to spillover of the endocannabinoids onto GABA synapses. Astrocytes, therefore, limit the actions of both orthograde and retrograde messengers spatially, and glial plasticity promotes synaptic crosstalk of messengers emanating from both presynaptic and postsynaptic cells.

Supported by NIH MH066958.