Title: Simulating the roles of cytokine signaling in the neural control of blood pressure

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Hypertension is characterized by a maladaptive inflammatory state – observed within the nucleus of the solitary tract (NTS) in the brainstem – involving aberrations in the levels of cytokines and chemokines. An inflammatory milieu in the NTS, a region associated with blood pressure set point control, is believed to elicit the development and/or maintenance of hypertension via overdrive of the sympathetic nervous system (SNS). The present work is focused on gaining a mechanistic understanding of how inter-cellular interaction dynamics in the NTS result in SNS overdrive. Towards this end, cellular models of microglia and astrocytes have been developed that include interactions amongst both anti- and pro-inflammatory cytokines, including GM-CSF, IL-1β, IL-6, TNFα, TGFβ, IL-10, and CCL5. Documented interactions between cytokines, such as the activation of IL-1β release by TNFα and the inhibition of TNFα release by TGFβ, have been incorporated into modified S-systems models in which input-output relationships/influences between cytokines are represented using Hill kinetics. Parameter estimation was based on cytokine responses to LPS observed in astrocyte and microglial cell cultures, and sensitivity analyses revealed the parameters most highly associated with model output variability. Perturbation simulations in which individual cytokines were stimulated, and the most responsive of the other cytokines were determined, yielded identities of common motifs embedded in the network. Information regarding cytokine dynamics following inflammatory stimuli will be applied to neuronal models containing ion channels known to show cytokine responsiveness, and effects of inflammation on electrophysiological excitability will be inferred in follow-up work. This model will generate specific predictions regarding the dynamic expression/regulation of inflammatory molecules and ion channels that can be tested at time-points throughout the course of hypertension development and maintenance. Experimental efforts are currently underway to measure developmental cytokine expression profiles in NTS tissue from control and hypertensive rat strains using a Luminex Flexmap 3D multiplex cytokine assay. Further, gene transcription measurements related to inflammation and electrophysiology are being obtained from glia, endothelial cells, and neurons in NTS tissue from control and hypertensive rats using a Fluidigm BioMark system. The combined results from these experiments will provide model validation and/or constraints for model re-calibration, along with the elucidation of temporal relations between inflammatory marker expression and blood pressure in control and hypertensive rats. The general aim of this approach, involving integration of experiment and computational modeling, is to identify control points for potential therapeutic treatment of hypertension.

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