CONTROLLING REACTIVE RESPONSES AROUND NEURAL PROSTHETIC DEVICES

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Reliable use of neural prosthetic devices is compromised by reactive responses that result in electrical isolation. Early reactive responses initiated by device insertion have many hallmarks of an inflammatory response and may be initiated by the process of device insertion, including unavoidable damage to the brain's microvasculature. Sustained responses develop as early responses wane. We have observed that sustained responses appear to result from tissue-device interactions and have been observed as long as three months following device insertions. To determine if altering inflammatory mechanisms can affect these reactive responses, we have examined the effects of peripheral and local applications of dexamethasone. This synthetic glucocorticoid activates specific receptors found in a variety of cells causing changes in gene regulation. Peripheral injections were made as subcutaneous injections in ethanol (200 μg/kg) and administered either as a single injection on the day of device insertion or for a total of six daily injections. Several limitations of this method are that long-term treatment requires repeated injections, drug exposure is episodic; and treatment does not specifically target the CNS. Local drug delivery, achieved by microfluidics or slow release of compounds from polymers, can overcome these shortcomings. In a first step to demonstrate the effectiveness of local, long-term release, ribbons of poly(ethylene-co-vinyl acetate) (EVAc) (~ 400 x 400 μm^2 and 2 mm long) containing dexamethasone (35% by weight) were inserted into premotor cortex of anesthetized 100-g rats using a 30-gauge needle. Immunohistochemistry and laser-scanning confocal microscopy were used to describe changes in astrocytes (GFAP), microglia (CD11b), and cells of the microvasculature (laminin) in 100 μm thick tissue slices. Samples were prepared one and six weeks following device insertions, representing the early and sustained responses, respectively. In general, reactive responses around control ribbons were similar to those observed around silicon devices with robust responses and accumulation of extracellular material immediately around inserted devices. Responses around control EVAc ribbons differed from those observed around silicon devices by the presence of large cavities. Dexamethasone treatment modified both early and sustained reactive responses. Peripheral injects resulted in greatly reduced astroglial responses, while microglial and vascular responses were either unaffected or increased. Local drug delivery using ribbons containing dexamethasone greatly attenuated all cellular responses of both early and sustained responses. At both times tissue closely packed around the ribbons, though relatively few cells were observed attached to ribbons. Dexamethasone release from EVAc ribbons decreased over time with significant amounts of release measured 40 days after initiation of measured release into physiological saline. Calculated drug concentrations drop off exponentially in the region immediately around insertion sites with initial areas of significant drug concentrations extending as far as several millimeters into the surrounding brain tissue. These results demonstrate that while peripheral injections of anti-inflammatory drugs can produce moderate effects on both early and sustained reactive responses following insertion of microfabricated prosthetic devices, local drug release may provide more complete and long-term control of cellular responses. Thus coating of devices with slow release materials or provisions for long-term drug infusion through microfluidic channels may provide a means to insure the chronic function of neural prosthetic devices.

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