INFLAMMATORY CELLULAR RESPONSE AND CYTOKINES IL-1β, IL-6 AND TNFα IN RAT AND HUMAN SPINAL CORD INJURY

by

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TABLE OF CONTENTS

RAT SCI EXPERIMENTS 66

ABSTRACT

The inflammatory response following spinal cord trauma plays an important role in the secondary SCI. The goal of this study was to characterize the posttraumatic inflammatory responses and localize cellular sources of IL-1β, IL-6 and TNF-α following SCI. Thus, we hypothesized that the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α may act as messengers to coordinate the inflammatory cascade in the secondary SCI and that the cytokine response should be greater in severe than in mild injury.

One hundred and twenty-six rats were used and rat spinal cord contusions were induced by the weight drop device. Mild and severe SCIs were respectively produced by dropping a 10-g weight from 3.0 and 12.0 cm. Inflammatory cellular responses were studied using immunohistochemistry and expressions of IL-1β, IL-6 and TNF-α mRNAs were analyzed by RT-PCR. Thirteen human spinal cords removed at autopsy were studied using immunohistochemistry and cellular sources of IL-1β, IL-6 and TNF-α were localized using double-label fluorescent confocal imaging.

In experimental SCI, neutrophils started to infiltrate primarily around blood vessels in the central gray matter at 6 hrs and peaked at 1 day. Macrophages were noted at 6 hrs and then progressively increased for the first 3 days postinjury. Activated microglia were found as early as 1 h after contusion and frequently wrapped around axonal swellings and healthy neurons. RT-PCR showed an early and robust up-regulation of IL-1β, IL-6 and TNF-α mRNAs in spinal cord after severe contusion injury, maximal at 6 h postinjury with return to control levels by 24 h postinjury, the changes being significantly less in mild injury. In human SCI, the inflammatory response paralleled the changes in experimental SCI, neurons and

microglia were identified as the cellular sources of IL-1β, IL-6 and TNF-α, and IL-1β co-existed with APP in the neurons and their axons.

RT-PCR analyses together with histological observations confirm that intrinsic CNS cells (neurons and microglia), not peripheral inflammatory cells, are the main source of cytokines because the peripheral inflammatory cells did not invade the injured spinal cord until 6 h postinjury, a time when cytokine mRNA levels had peaked and started to decline. Microglia around axons may have their possible beneficial effects on the injured axons by providing a trophic local environment to promote the regeneration of the injured axons and the co-existence of IL-1β and APP indicates a possible role of IL-1β in the production of APP. Furthermore, our comparative RT-PCR analyses, showing significantly increased expression of pro-inflammatory cytokine mRNAs in severe injury in contrast to mild injury, support the hypothesis that cytokine up-regulation is an important factor in the generation of the severity of the inflammatory response and thus a suitable target for pharmacological intervention to attenuate this response.