Validation of a Rodent Model of Chemotherapy-Induced Peripheral Neuropathy Using Oxaliplatin

Smith J (1), Ripsch MS (1,2), White FA (1,2)

- (1) Anesthesia, Indiana University School of Medicine Indianapolis, IN
 - (2) Richard Roudebush VA Medical Center, Indianapolis, IN

Oxaliplatin (OXPL) is one of the most widely used and effective chemotherapeutic agents for colorectal cancer. However, the drug therapy is accompanied by severe dose-limiting off-target effects including tingling, burning pain and mechanical allodynia in the extremities of patients; together these symptomology is better known as chemotherapy-induced peripheral neuropathy (CIPN). The underlying pathophysiological mechanisms of CIPN are poorly understood and current therapeutic options only serve to alleviate the symptoms rather than prevent CIPN. To better understand mechanisms of OXPL-induced CIPN (OXPLN), we exposed adult female Sprague-Dawley rats to four intraperitoneal injections of vehicle or OXPL on alternative days. Behavioral results showed that thermal sensitivity failed to be affected by the OXPL. In contrast, the magnitude of mechanical allodynia increased such that the baseline withdrawal threshold for drug-treated animals was significantly lower than that for unprimed animals. Application of OXPL to afferent sensory neurons produced an increased amplitude and duration of compound action potentials that could be reversed with the voltage-gated sodium channel blocker, carbamazepine (CBZ). Astroglial and microglial markers glial fibrillary acidic protein (GFAP) and Iba-1 were imaged to examine glial reactivity in OXPLN at day 14. Microglia were not activated following OXPL whereas astrocytes exhibited increased GFAP fluorescence which paralleled OXPLN. Activation of astrocytes was prevented by co-administration of CBZ. These observations suggest that CBZ may serve to diminish OXPLN in the patient population.