**Understanding the pathogenesis of oxaliplatin-induced peripheral neurotoxicity**

1)Riva BR. 2)Potenzieri AP. 3)Lim DL. 4)Dionisi MD. 5)Carozzi CV. 6)Cavaletti G. 7)Distasi CD. 8)Genazzani AG.

*Dipartimento di Scienze del Farmaco*

Peripheral neurotoxicity is a limiting problem during oxaliplatin (OHP) chemotherapy so that most of cancer survivors have to deal with a severely compromised quality of life. OHP treatment produces an acute sensory neuropathy with allodynia, dysesthesia and burning neuropathic-like pain and a chronic sensory syndrome with enduring characteristics. In the last years, preclinical evidence raised the hypothesis that intracellular calcium-related events might play an important role in the onset of oxaliplatin-induced peripheral neurotoxicity (OIPN) in dorsal root ganglia (DRG), but the results of mechanistic studies appear somewhat inconsistent. Recently, research has investigated the effects of OHP on the activity of plasma membrane calcium channels, which are known to participate in the transduction of noxious stimuli. In particular, the transient receptor potential (TRP) channels, a heterogeneous class of cation channels that may be seen as cellular sensors activated by a variety of physical, mechanical, thermal or chemical stimuli. The major focus of investigation in this area related to OHP have been TRPV1, TRPM8 and TRPA1. Thus, we tested the functional effects of OHP on these cation channels in DRG neurons of Balb-c mice. First, by calcium imaging approach we observed that, an acute treatment with OHP (6 hours 0.1 μg/mL) reduces the responses to TRPV1 agonist (200 nM capsaicin), but significantly enhances the responses to TRPA1-M8 agonist (1μM icilin). In detail, we demonstrated that OHP increases icilin responses by TRPA1-dependent mechanism, since: (i) co-stimulation with icilin and a TRPV1-M8 antagonist (3 μM BCTC) does not impair the effects induced by icilin alone; (ii) co-stimulation with icilin and TRPA1 specific antagonist (10 μM HC-030031) completely abolishes the responses to TRPA1 agonist. Furthermore, according to recent literature that postulated a close relationship between the activation of TRPV1-M8-A1 channels and intracellular pH, we assessed that OHP induces a significant intracellular pH acidification in DRG neuros, as compared to control conditions. In order to understand whether the effects on icilin responses and intracellular pH were specific for OHP or even related to other platinum chemotherapy drugs, we also evaluated the responses induced by cisplatin and carboplatin. We have shown that both drugs, at the same concentration of OHP, are not able to enhance icilin responses and modify intracellular pH. Recent literature speculates that the presence of intracellular oxalate, a metabolite of OHP, would lead to a change in both sodium and calcium voltage-operated channels and to a disruption of intracellular free calcium. In order to establish the effects induce by oxalate on icilin responses and intracellular pH, we treated DRG neurons with oxalate alone or in combinations with OHP at the same concentration for 6 hours. Our experiments have shown that oxalate does not reproduce the same effects of OHP and surprisingly we observed that co-treatment with these two drugs completely abolishes the effects induce by OHP alone, as regards both the responses to icilin and the acidification of intracellular pH.

Conclusion: OHP induces the acidification of intracellular pH in DRG neurons. This effect results in TRPA1 activation and TRPV1 inhibition. Oxalate and other platinum chemotherapy drugs are not

able to reproduce the same effects. The co-treatment with oxalate and OHP completely abolishes the effects induce by OHP alone.