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LETTER TO THE EDITOR

The contribution of SK3 polymorphisms to acute oxaliplatin-induced neurotoxicity: direct or indirect effects?

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Dear Editor,

We read with interest the manuscript by Basso and colleagues recently published in Cancer, Chemotherapy and Pharmacology [1] regarding the association between polymorphisms in K^+ channel genes and acute oxaliplatin-induced neurotoxicity. The authors identified polymorphisms in SK3, the small-conductance calcium-dependent K^+ channel, which were associated with severity of neurotoxicity. Patients with severe acute neurotoxicity were more likely to have a shorter CAG repeat and accordingly a less efficient K^+ channel. The study suggested that oxaliplatin may interfere with SK3 channel function via impairment of tetramer formation. However, there is no evidence to suggest that oxaliplatin modulates K^+ channel tetramerization nor to suggest that direct modulation of K^+ channel function is the chief mechanism of oxaliplatin-induced neurotoxicity.

In contrast, a number of studies have suggested a role for Na^+ channel dysfunction in the etiology of acute oxaliplatin-induced neurotoxicity. Specifically, recent studies identified significant abnormalities in axonal Na^+ channel function in patients acutely following oxaliplatin [2–4]. In further support, in vitro studies have also demonstrated the effects on Na^+ channels, typically via changes in the kinetics or voltage dependence of Na^+ channel inactivation [5–9]. In contrast, the literature on the effects of oxaliplatin on K^+ channels appears conflicting. While a number of studies have ruled out any role of oxaliplatin in the modulation of K^+ channel function [5, 7, 10], some in vitro studies have identified the effects on K^+ channels [8, 9, 11], although typically in combination with abnormalities in Na^+ conductances [8, 9]. Of further relevance, oxaliplatin was markedly less effective in blocking K^+ channels than Na^+ channels [8]. Accordingly, there is no defined causal role of K^+ channels in the etiology of oxaliplatin-induced neurotoxicity.

In human axons, slow K^+ channels are involved in controlling the response to repetitive activity, rather than in repolarization following conduction of a single action potential [12]. Importantly, denervation produces upregulation of SK3 channels and is associated with repetitive activity and hyperexcitability [13]. However, denervation-induced hyperexcitability requires SK3 channel expression in addition to changes in other ionic conductances such as Na^+ channels to "unlock" the effects of SK3 channels in facilitating hyperexcitability [13]. It remains plausible that SK3 polymorphisms modulate the severity of oxaliplatin-induced neurotoxicity by producing less active SK channels. As such, reduced functionality of SK channels may contribute to enhanced oxaliplatin-induced hyperexcitability in the absence of a direct effect on K^+ channels. Of further interest, the K^+ channel activator flupirtine has successfully suppressed oxaliplatin-induced hyperexcitability using an in vitro model [14]. Importantly, this approach may be successful independent of the molecular basis of oxaliplatin-induced neurotoxicity, by harnessing slow K^+ conductances in dampening hyperexcitability.

The early identification of patients at risk of severe neurological sequelae following oxaliplatin treatment remains an important and emerging research area. This is particularly the case in the adjuvant setting, where long-term

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neuropathy is clearly an unacceptable outcome. Perhaps the most important consideration from the study by Basso and colleagues would be to compare SK3 polymorphisms with neurological status following oxaliplatin treatment, to assess whether the acute neurotoxicity is related to long-term neuropathy. Improved understanding of the complex mechanisms underlying development of both acute and chronic oxaliplatin-induced neuropathy is of central importance in tackling this challenging clinical conundrum.

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