Novel Strategies for Translational Research in Pain Drug Discovery

Andre Ghetti
AnaBios Corp., San Diego, CA 92109, USA

As pain therapeutic targets, ion channels provide several attractive features, including human genetics-based evidence of involvement in pathological states, tissue-specific expression patterns and proven druggability. Several ion channel types have been implicated in normal pain perception as well as pathological pain states. Human genetic studies have provided evidence for the role of voltage gated sodium channel (VGSC) subtypes in pain signaling and for a key role of mutations in these channels in several chronic pain conditions. Single-gene mutations have been described that lead to sensory neurons hyper- or hypo-excitability resulting from altered properties of specific VGSC channels. In addition, other classes of ion channels have emerged as important contributors to nociception and chronic pain and represents potentially valuable targets.

Despite these advances, it remains unclear how the various channel classes are implicated in different forms of chronic pain. This knowledge gap is one of the impediments to the identification of the most appropriate molecular selectivity for analgesic drugs directed towards a specific pain pathology.

Compounding the problem, the translation from preclinical animal pain models to humans has been has been unreliable at best. Cross-species difference in pharmacological response and analgesic effects are now well documented and extremely common. A novel preclinical discovery strategy, which relies on human sensory neurons isolated from organ donors, has recently been introduced. Human sensory neurons-based models overcome the cross-species translational challenges commonly encountered with animal models. In addition, this approach can be used to study the effects of new pain drug candidates in the context of different pain types thereby providing critical data to predict the most appropriate pain indication for a specific compound.