# Screening an in house alkaloids library using Voltage-Sensor Probes for new modulators of voltage-gated sodium channels

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| Auteur | Coquerel, Quentin [1], Le Ray, Anne-Marie [2], Mattei, César [3], Guérineau, Nathalie C [4], Bréard, Dimitri [5], Siegler, Benjamin [6], Richomme, Pascal [7], Legros, Christian [8] |
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| Résumé en anglais | Voltage-gated sodium channels (Nav) are molecular targets of clinically used drugs for treatments of various diseases (epilepsy, chronic pain, cardiac arrhythmia…) and also of numerous animal and plant neurotoxins. The development of easy-to-use screening assays for searching new ligands from chemicals libraries, animal venoms or plant extracts represents a challenge of a great interest to generate therapeutic hits. Here, we used the mammalian GH3B6 pituitary cell line, which constitutively expresses three different neuronal Nav channel isoforms (Nav1.2, Nav1.3 and Nav1.6), to identify novel compounds of pharmacological interest from a library of in-house vegetal alkaloids. The screening is based on a method using Voltage-Sensor Probes (VSPs) that we adapted to detect both activators and blockers of Nav channels. Over the 84 pure alkaloids or plant extracts that were screened, 17 increased the VSP signal. They operated as gating modifier, showing an action mechanism similar to that of batrachotoxin (BTX), known to strongly inhibit Nav channel inactivation. The remaining 67 plant products were assessed for their potency to inhibit BTX-induced VSP signal. We further selected 11 alkaloids as efficient Nav channels inhibitors. We focused our attention on two structural analogs belonging to the aporphine family, liriodenine and oxostephanine, which differ only by a methoxy group. Whereas liriodenine has been already described as a Nav channels blocker, oxostephanine has not been yet documented as an ion channel modulator. In conclusion, the novel VSPs-based screening assay we developed is a suitable method to challenge the discovery and to assess the activity of novel ligands on Nav channels. |
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