Discovery of Novel Natural Products Targeting Ion Channels

Yin Nian
Key Laboratory of Animal Models and Human Disease Mechanisms, and Ion Channel Research and Drug Development Center, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming 650223, P. R. China

Natural products (NPs), including those from traditional Chinese medicine, are a rich source for mining active compounds or drugs against diverse human targets, including on channels (ICs). To search for natural compounds that target ICs, we have constructed a battery of ion channels crucial for the human disease and established various ion channel screening platforms with diverse and complementary capabilities. Up till now, more than 1200 natural compounds have been screened on Ca_v, K_v, Na_v, TRP, and ASIC channels. As a result, we have identified a number of novel compounds acting on $Ca_v3.1$ T-type calcium channels, $Ca_v2.2$ N-type calcium channels, $K_v1.3$ potassium channels and so on. For instance, (**1**) (±)-Cochlearoids A (**1**) and D (**2**), and (±)-Cochlearines A (**3**) are novel meroterpenoid enantiomers from *Ganoderma lucidum* (known as almighty "Linzhi" in China). Compounds (+)-**1**, (−)-**2** and (±)-**3** are potent (as strong as positive control, Mibefradil) and selective $Ca_v3.1$ inhibitors; (**2**) Jatamanvaltrate T (**4**) and Valtratehydrin B8 (**5**) are two iridoids from an analgesic herb, *Valeriana jatamansi*, using bioassay guided method. Compounds **4** and **5** inhibited $Ca_v2.2$ with an EC_{50} of 3.3 μM and 7.0 μM, respectively, and weakly inhibited $Ca_V1.2$ and $Ca_V3.1$, but it had no effect on Kv1.2, Kv2.1, Kv3.1, BK and $Ca_V2.1$channels; (**3**) pepluacetal (**6**) and pepluanol A-B (**7**−**8**) are three highly modified diterpenoids from *Euphorbia peplus*, an anti-psoriasis herb. All three compounds inhibit Kv1.3, with compound **6** being the most eff ective with an IC_{50} value of 9.50 μM.

More significantly, we have also identified a compound named AA-1 from *Stephania Yunnanensis* that demonstrates outstanding antiarrhythmic effects. In heterologous expression systems, AA-1 inhibited a variety of cardiac ion channels, including voltage-gated sodium, potassium and calcium channels. Remarkably, AA-1's antiarrhythmic effect is better than that of lidocaine and amiodarone, positive controls used in our studies. Moreover, even at a high dose of 5 mg/kg it does not affect normal heartbeat and does not induce long QT (induction of long QT is a side effect of some existing antiarrhythmic drugs). Now, we focus on how synergistic actions of AA-1 on multiple channels bring about its potent antiarrhythmic effect; and determine AA-1's toxicity and pharmacokinetic properties.

Our studies uncover several chemically distinct $Ca_v3.1$ and $Ca_v2.2$ and Kv1.3 inhibitors from NPs, highlighting the potential of discovering more novel natural molecules that target ICs. Besides, NPs also provide the potential of the development of new antiarrhythmic medicines in China.