Pharmakodynamic Analysis of Electrophysiological Data for Voltage-Gated Sodium Channels

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0.1 Drug Binding to Inactivated States

Determination of the dissociation constant from a *drug-bound* to a *slow inactivated* state, as sketched in fig. 1 panel B and C. *Model B* is difficult to identify. In *model C*, drug-bound states (fast *ID* and slow *SD*) are lumped into a single state *D*. In this model the apparent dissociation constan from $D \leftrightarrow S$ is identifiable via a concentration-response relationship as derived below.

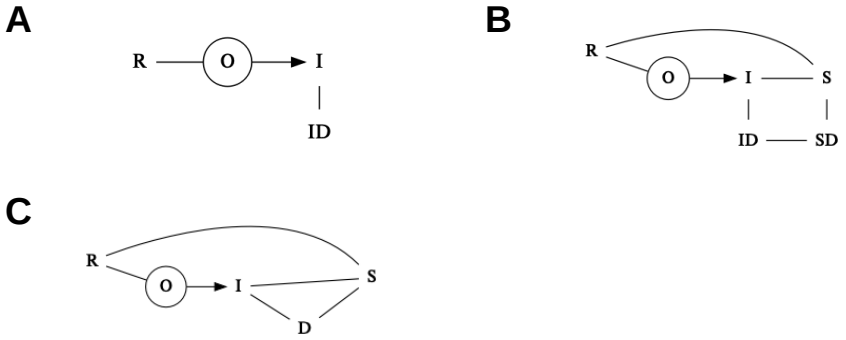

Figure 1: State models for drug-binding to Na_V channels. A) Channel with only one fast inactivated state. B) Channel with a fast and slow inactivated state.

Only the fraction of channels that are in the *fast inactivated state* after the inactivation pulse are recovered into an activatable *resting state R* by the recovery pulse (20 ms duration). Subsequently only these mediate a current upon the test pulse. According to the model in fig. 1C, the following relationships for the amplitudes of control (I_C) and drug-bound channels (I_D) during the subsequent test pulse are proposed

$$ {}^{0}I_C = {}^{0}I_D = ([R] + [S] + [SD_n]) \cdot \bar{i}_{Na} \tag{1a} $$

$$ {}^{\infty}I_C = ([R] + [SD_n]) \cdot \bar{i}_{Na} \tag{1b} $$

$$ {}^{\infty}I_D = [R] \cdot \bar{i}_{Na} \tag{1c} $$

with the fractional current $\bar{i}_{Na}$

$$ \bar{i}_{Na} = \hat{g}_{Na} \cdot (V_P - E_{Na}) \tag{2} $$

Here, ${}^0I_C$ and ${}^0I_D$ represent control currents and currents for cells exposed to drug, respectively, at a inactivation impulse duration of $t = 0s$, or ${}^\infty I_C$ and ${}^\infty I_D$ after very long inactivation duration ($t \to \infty s$, i.e. steady-state). Symbols in square brackets indicate the "concentration" of channels in corresponding states after this infinitly long inactivation pulse. So, $[R] + [S] + [SD_n]$ represents the total amount of channels. The dissociation constant for drug binding to channels in the *slow inactivated* conformation is described by

$$S + nD \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} SD_n \tag{3}$$

Therefore it holds that

$$K_S = \frac{[S] \cdot [D]^n}{[SD_n]} \tag{4}$$

According to Hill and Langmuir K_S determines the ratio of *drug-occupied* to *total amount of channels* in state S or alternatively *drug-free* to *total amount of channels*

$$\begin{aligned} y &= \frac{\textit{drug-free channels in state } S}{\textit{total number of channels in state } S} \\ y &= \frac{[S]}{[S] + [SD_n]} \end{aligned} \tag{5}$$

Rearranging eq. 4, substitution into eq. 5 and simplification gives the following Hill equation

$$y = \frac{K_S}{K_S + [D]^n} \tag{6}$$

The ratio y can be expressed from measured currents in eqq. 1 as follows

$$y = \frac{{}^0I_C - {}^\infty I_C}{{}^0I_D - {}^\infty I_D} \tag{7a}$$

$$= \frac{[R] + [S] + [SD_n] - [R] - [SD_n]}{[R] + [S] + [SD_n] - [R]} \tag{7b}$$

$$= \frac{[S]}{[S] + [SD_n]} \tag{7c}$$

From eq. 6 and eq. 7a

$$\frac{{}^0I_C - {}^\infty I_C}{{}^0I_D - {}^\infty I_D} = \frac{K_{bS}}{K_{bS} + [D]^n} \tag{8}$$

Therefore, K_{bS} could be estimated by fitting eq. 8 to currents measured according to the *block-entry protocol*. K_{bS} represents the *dissociation constant* as determined from a functional assay, which is equal to K_S if the expression in 7b were correct.