Interaction of local anesthetics with a peptide encompassing the IV/S4-S5 linker of the Na$^+$ channel.

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The interaction of two local anaesthetics (LA): lidocaine and benzocaine, with the peptide pIV/S4-S5 encompassing the cytoplasmic linker between helices S4-S5 in domain IV of the voltage-gated Na$^+$ channel, residues 1644-1664, has been studied by DOSY, hetero-nuclear NMR $^1$H-$^{15}$N-HSQC spectroscopy and computational methods. DOSY indicates that benzocaine, a neutral ester, exhibits a stronger interaction with pIV/S4-S5 than lidocaine, a charged amine-amide. Weighted averaged chemical shifts, $\Delta \delta(^1$H-$^{15}$N), show that benzocaine affects L$^{1653}$, M$^{1655}$ and S$^{1656}$ while lidocaine slightly perturbs the I$^{1646}$, L$^{1649}$ and A$^{1659}$, L$^{1660}$, near the N and C-terminus, respectively. Computational methods confirmed the stability of the binding of benzocaine and the existence of two binding sites for lidocaine. In summary our data support the hypothesis of the existence of multiple LA binding sites in the IV/S4-S5 linker. In addition, since this linker is part of the receptor for the "inactivation gate particle", the knowledge that LA can bind to that region with diverse binding modes and strength may provide a key to better understand, at a molecular level, the various aspects of LA pharmacological activity and of Na$^+$ channel functionality.