LA potency: Physical characteristics

Classically, potency, speed of onset, and duration of action are related to a local anesthetic's lipid solubility (more lipid soluble = more potent), pKa (lower = faster), and protein binding (more binding = longer duration of action). However, there is some overlap in this and other modifying factors.

Local anesthetics are weak bases whose dissociation can be expressed as:

$$LAH^+ \leftrightharpoons LA+H^+$$

and

$$pKa = \log([H^+][LA]/[LAH^+])$$

With the exception of benzocaine, all local anesthetics have a pKa >7.4 and exist primarily as the charged, base form at physiologic pH. This charged form is the active form that better interacts with the sodium channel, however the anesthetic must first cross the uncharged cellular membrane as the site of action is intracellular. Local anesthetics do this most readily in their neutral state which is why a lower pKa results in a faster onset (local anesthetic can more readily get to the site of action). Similarly, the more lipid soluble a drug, the greater proportion of it will get to the intracellular portion of the sodium channel and therefore the more potent the drug (also the faster onset of action, although pKa likely has a larger effect). Coincidentally, lipid soluble drugs tend to be more protein bound and are therefore less available to a patient's metabolic machinery, hence the prolonged duration of action.

Of course we can tweak some of these variables by adding bicarbonate (increases pH of injectate, more local anesthetic is uncharged, faster onset of action), using a higher concentration (3% 2-chloroprocaine, fastest onset of action despite the highest pKa of 9.1), or adding a vasoconstrictor (which reduces uptake into the bloodstream, prolonging duration of action for certain local anesthetics).

I have seen conflicting information about the effect of molecular weight on potency. I have seen that smaller molecules can diffuse across the cellular membrane faster and therefore increase speed of onset. I have also seen that increasing molecular weight increases potency. I have been unable to find the primary source for this second statement, but it seems to stem from a study where they looked at potency of different local anesthetics modified by adding carbon atoms. This would also increase the lipid solubility of a molecule and perhaps this is the driving force behind the increase of potency, but if anyone has good information on the effect of molecular weight on local anesthetics pharmacodynamics, I would love to see it.

Further reading: Hemmings, HC, Egan, TD. Pharmacology and Physiology for Anesthesia, 2nd ed. "Local Anesthetics". 20:390-411. Elsevier: 2019

NYSORA: https://www.nysora.com/topics/pharmacology/clinical-pharmacology-local-anesthetics/