LOCAL anesthetics are familiar to all anesthesiologists. They canonically inhibit the alpha subunits of voltage-gated sodium channels within electrically excitable tissues. The ability to diminish the propagation of electrical signals through neurons and cardiac muscle forms the basis of their use in regional anesthesia and their arrhythmogenic cardiac complications, respectively. Yet empiric data have long suggested that local anesthetics also have antiinflammatory and antiapoptotic effects. These observations have been corroborated in preclinical models including those focused on the immune response to ischemia-reperfusion injury, a common pathology across our perioperative and critical care patient populations. The extent to which local anesthetics provide beneficial antiinflammatory effects and whether voltage-gated sodium channels are bona fide therapeutic targets for antiinflammatory interventions are open and intriguing questions for clinicians and scientists alike. As such, the role of these channels in immune cells remains an active area of research.

In this issue of Anesthesiology, Poffers et al. evaluate the role of neutrophil voltage-gated sodium channels in preclinical models of ischemia-reperfusion injury, providing further evidence for the functional importance of these ion channels within immune cells. Voltage-gated sodium channels comprise a family of nine alpha subunits (referred to as NaV1.1 through NaV1.9), which are variably expressed in leukocytes. For example, NaV1.5, the predominant voltage-gated sodium channel within cardiac myocytes, regulates intracellular acidification processes as well as pathogen phagocytosis in macrophages. It is unlikely, however, that the function of NaV1.5 in macrophages alone explains the immune-modulating effects of local anesthetics in ischemia-reperfusion injury, and neutrophils have been proposed as the primary antiinflammatory target of local anesthetics. The myocardial injury sustained with ischemia and reperfusion is strongly associated with neutrophil recruitment and activation in the heart, which can be partially protected by reducing neutrophil accumulation within the area of injury.

The work presented by Poffers et al. lends further support to this focus on neutrophils. They demonstrate that while both human and mouse neutrophils express multiple voltage-gated sodium channel alpha subunits, neutrophils recruited to ischemic cardiac and renal tissue specifically express NaV1.3. Accompanying studies implicate voltage-gated sodium channels in neutrophil adhesion, transmigration, and chemotaxis—all fundamental to the neutrophil inflammatory response—but do not implicate them in reactive oxygen species production. While specific pharmacologic inhibitors of the various alpha subunits are lacking, Poffers et al. cleverly combined nonspecific inhibitors in their functional studies. Importantly, lidocaine reduced both neutrophil adhesion and transmigration.

The observation that a subset of neutrophils recruited to the site of injury expresses NaV1.3 suggests that this subunit may represent a therapeutic target for ischemia-reperfusion injury. It would have been informative to establish whether the inhibition of NaV1.3 or other voltage-gated sodium channels impacts immune cell infiltration, infarct size, and organ function in their models of cardiac and kidney injury.

Moving forward, the subpopulation of neutrophils that express NaV1.3 within the injured tissue requires careful characterization in order to determine what promotes their preferential recruitment. To that end, Poffers et al. suggest that neutrophil adhesion itself and not the proinflammatory mediators released during injury may trigger the upregulation of NaV1.3. However, the signaling pathways that link neutrophil adhesion to voltage-gated sodium channel expression are unknown. Similarly, how NaV1.3 modulates neutrophil cellular function requires delineation, especially when considering that standard electrophysiologic studies were unable to capture significant voltage-gated sodium channel activity within neutrophils. As the authors suggest,
this may signify an intracellular localization for NaV1.3, as has been shown of NaV1.5 in macrophages.4 The role of the voltage-gated sodium channel beta subunit may equally play a role in modulating neutrophil function and should be investigated.

Together, these additional studies would allow us to ascertain whether lidocaine and other local anesthetics exert immune-modulating effects by targeting neutrophil voltage-gated sodium channels. This is particularly important given that previous investigations suggest that the antiinflammatory properties of local anesthetics may be independent of sodium channel inhibition. More broadly, should voltage-gated sodium channels be therapeutically targeted in inflammation and ischemia-reperfusion injury?

Pharmacologic inhibitors of voltage-gated sodium channels have a long-standing and familiar history in anesthesia. A few years after the isolation of cocaine, the first local anesthetic, Claude Bernard made his prescient remark that “L’anesthésique n’est donc pas un poison spécial du système nerveux, il anesthésie tous les éléments, tous les tissus en engourdissant, en arrêtant momentanément leur irritabilité nutritive” (“An anesthetic is not a special poison for the nervous system, it anesthetizes all the elements, all the tissues, and stopping temporarily their irritability”).7 This statement foreshadowed our rapidly evolving molecular understanding of the impact of local anesthetics and their targets in a diverse group of nonexcitable tissues. The paucity of work addressing voltage-gated sodium channels within nonexcitable tissues such as immune cells should prompt us to consider other potential indications for these medications. As the pleiotropic roles of these channels in immunity are further elucidated, it is becoming increasingly evident that this family of proteins represents a potential therapeutic focus of immune modulation. The development of new local anesthetics or other novel medications directed at voltage-gated sodium channels—targeting neutrophil NaV1.3, for example—will be greatly informed by preclinical studies of voltage-gated sodium channels in nonexcitable tissues and may ultimately add to the anesthesiologist’s antiinflammatory armamentarium. To that end, NaV1.3 is particularly notable as it has also been implicated in neuropathic pain secondary to nerve injury and diabetic neuropathy.8,9

In closing, Poffers et al. explore the molecular basis for the actions of the drugs that are the foundation of our clinical specialty and, in doing so, may ultimately expand our professional practice and better help our patients.

Competing Interests

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