Molecular Basis of Neural Blockade

In this issue, Strichartz reviews the molecular basis of neural blockade by local anesthetics. As anesthesiology becomes more the topic of the clinician, it is both timely and pertinent to his practice. It is timely because he may see a swing back to regional anesthesia now that halogenated inhalation anesthetics seem to present unanticipated biologic hazards. It is pertinent because understanding how and where local anesthetics act will help him troubleshoot the occasional failed block.

Though there is little to add to (and nothing to subtract from) Strichartz's review, "putting it all together" into a cohesive chart to point out the key landmarks on the course may serve a useful purpose.

The central theme of neural blockade is that local anesthetics occlude the sodium channels of nerve membranes, preventing the generation of an action potential; the nerve, in other words, is rendered inexcitable. While other modes of action have been postulated (e.g., calcium ion competition, surface charge alteration) none but the sodium channel occlusion hypothesis has survived rigorous testing.

How local anesthetics occlude membrane sodium channels gets a bit more complicated; it requires a brief side trip to theory. As may be recalled, local anesthetic amines lead a double life. In aqueous surroundings, the anesthetic salt dissociates into a protonated positively charged quaternary amine, the cation, and an electrically neutral uncharged tertiary (rarely, secondary) amine, the base. Cation and base are in dynamic equilibrium, the proportions of each species being governed by the dissociation constant of the local anesthetic, and by the hydrogen ion concentration of the medium.

The anesthetic cation—by virtue of its positive charge—contributes the lion's share of blocking activity, for it binds to anionic receptors associated with the gating structures of the sodium channels. The gates are glued shut, figuratively speaking, so that the sodium channel is plugged by the local anesthetic molecule. A factor of considerably lesser importance, invoked mainly to explain blockade by benzocaine, is that the neutral anesthetic species must possess some blocking action, weak as it may be. The most satisfactory explanation for how the local anesthetic base acts is that it causes the nerve membrane to swell (as lipid-soluble general anesthetics reputedly do). Such swelling, in turn, is thought to pinch the transmembrane sodium channels shut, and so bar sodium passage. Where along the transmembrane channel the local anesthetic cation nestsles is not altogether certain, though a reasonably specific visualization can be provided. It turns out that local anesthetics of the procaine and lidocaine families bind to the internal (axoplasmic) mouth of the sodium channel, where they glue the gating functions in the closed position. Since the local anesthetic molecule is much too bulky to traverse the slender sodium channel, it must first diffuse through the lipid framework of the membrane before it can
reach its target. That complicates matters, as the cation’s very charge virtually imprisons it when diffusion barriers block the way. The task of diffusion falls to the lipid-soluble neutral base, which carries the local anesthetic molecule through the membrane. In short; the cation is the molecular species that plugs the channel, but the molecule must first be in the base form to get there.

Certain channel-blocking marine toxins (tetradotoxin, for instance) circumvent this handicap in that they bind to receptors located near the entrance to the sodium channel, where it faces the extraneuronal environment. Derivatives of these drugs thus may well turn into useful blocking agents, since they do not have to rely on transmembrane diffusion to reach the internal action locus—as conventional local anesthetics must do.

Finally, a few words about “use-dependent inhibition,” a topic detailed at some length in the review article. While intensity of (and recovery from) experimental blockade may be varied to some extent by manipulating the frequency of stimulation, the phenomenon’s clinical relevance remains to be seen.

With the landmarks now well in sight, the reader can all the better savor the technical niceties and experimental subtleties of Strichartz’s polished review article.

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Control of Respiration

OBESITY AND RESPIRATORY DRIVE
In some markedly obese patients, respiratory response to carbon dioxide is significantly decreased. Can this abnormality be reversed by dietary manipulation? The authors have studied 18 obese patients (six with the obesity-hyperventilation syndrome and 12 with normal CO2 responses). Pulmonary function, blood gases, serum ketone levels, and ventilatory response to CO2 were evaluated at three times: 1) Control period of 3–5 days during which patients were maintained on a 2,500-kcal diet (40 per cent carbohydrate, 40 per cent fat, 20 per cent protein); 2) Ketosis was induced for 3–7 weeks by fasting (13 subjects) or a 400-kcal diet of protein (five subjects); 3) Patients were re-fed with a 1,000–1,200-kcal diet for 7–10 days. Studies were performed at the end of each phase. Changes in weight were similar in the hypoventilating and control groups. CO2 sensitivity was unaltered by ketosis in the obese controls. However, in the hypoventilating group, CO2 response was more than doubled in the ketotic phase (0.8 ± 0.1, 1.8 ± 0.2, 0.9 ± 0.1 liter/min/torr in the three phases). This improvement could not be related to changing weight, pulmonary function, arterial blood pH, or differences in ketosis between the two groups. There was a significant relationship between CO2 response and ketone-body concentration in the hypoventilating subjects. The authors conclude that the decreased ventilatory response to CO2 occurring in some obese patients may be returned toward normal by dietary manipulation. (Fried PI, and others: Effect of ketosis on respiratory sensitivity to carbon dioxide in obesity. N Engl J Med 294: 1081–1086, 1976.)