Noradrenergic Trespass in Anesthetic and Sedative States

In this issue of Anesthesiology, Hu et al.1 delve into the mechanisms of hypnotic action of potent volatile anesthetic agents as well as dexmedetomidine; these data build upon previous work from this and other laboratories that collectively provide insights that may affect how these agents are used in clinical practice.2-8 Using mice that lack the dopamine-β-hydroxylase (DBH) gene and are therefore incapable of synthesizing noradrenaline and adrenaline throughout the organism, the authors confirm their previous findings of enhanced sensitivity to, or delayed emergence from, volatile anesthetic agents.2 In addition, they corroborate that α1 adrenergic agonists (of which dexmedetomidine is the prototype in contemporary clinical practice) are capable of producing a hypnotic response, established both by behavioral and electrophysiological paradigms, in these mutated mice. Further, they show that DBH knockout mice are remarkably sensitive to dexmedetomidine, using more sophisticated electrophysiological endpoints than the previously reported loss of righting reflex.1 Ultimately Hu et al.’s interpretation of their data challenge the Nelson model of anesthetic action for dexmedetomidine,7 but not GABAergic agents,3,6,8 which centers on suppression of noradrenergic signaling from the locus ceruleus (fig. 1). Earlier, these investigators established that both GABAergic agents and dexmedetomidine activate the ventrolateral preoptic nucleus, the endogenous sleep switch; however, they proposed that dexmedetomidine appeared to do this by inhibiting noradrenergic input from the locus ceruleus into the ventrolateral preoptic nucleus while GABAergic agents act directly on ventrolateral preoptic nucleus itself.

Mice that lack a critical gene, such as DBH (DBH−/−), survive the absence of critical neurotransmitters by adaptive changes. In DBH−/− mice, there is a significant increase in the catecholamine dopamine, the substrate for the absent enzyme, which is also capable of binding to and activating both adrenergic and noradrenergic receptors, although with much lower affinity.9 The authors acknowledge this possibility, and devise a “reversal” experiment in which adrenergic and noradrenergic ligands are administered centrally, using a pharmacological strategy developed by one of the authors1; this normalizes the sensitivity of DBH−/− mice to that seen in the wild-type control mice. However, to establish that this is solely due to replenishing the missing ligands, it would be necessary to show that this pharmacologic strategy does not nonspecifically alter sensitivity in wild-type mice that already have a full complement of catecholamines. In the absence of such data, one cannot conclude that pharmacological restoration of noradrenaline and/or adrenaline in the DBH−/− mice is the reason for normalization of the sedative response to dexmedetomidine.

Regarding the overexpression of dopamine, by binding and activating the D2 dopaminergic receptor subtype, this catecholamine is capable of decreasing the minimum alveolar concentration for halothane10; whether or not a similar alteration in sensitivity obtains for α1 agonists is known. Remarkably, others have shown enhanced reversal of the hypnotic response to iso-flurane with increased dopaminergic signaling.11 Both alternatives need to be directly addressed if one is to conclude that the enhanced sensitivity is due to the missing ligands, rather than due to the increased expression of dopamine.

Notwithstanding these issues, data provided in this article contribute to an impressive body of work from Kelz’s laboratory,

“If substantiated, suppression of noradrenergic signaling would emerge as a core component of anesthesia to prevent the awareness of surgery.”

Photo: J. P. Rathmell.

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Anesthetics that act on GABAergic agents type A receptors, such as propofol, pentobarbital, and the volatile anesthetics, exert little effect on noradrenergic signaling (fig. 1). Nevertheless, attenuation of noradrenergic signaling does increase sensitivity to GABAergic agents (as Hu et al. illustrate). Suppression of noradrenergic signaling does not appear necessary for anesthetic-induced hypnosis (defined as the patient “looking asleep”) paralleling its redundancy in the sleep–wake cycle. However, while the patient may look “asleep,” intact noradrenergic signaling may drive connectedness to the environment explaining why hypnotic doses of anesthesia always do not suppress responses on the isolated forearm technique during surgery. As such, noradrenergic signaling may be considered a previously unrecognized trespasser in the anesthetic state, which may promote awareness during GABAergic hypnosis.
Delaying connectedness on emergence from hypnosis may have related consequences such as reducing postoperative and critical care delirium by preventing emergence from hypnosis at a reduced level of consciousness. This state can be considered akin to “sleep inertia” in which subjects awake confused from nonrapid eye-movement sleep; similarly, delirious patients may not have sufficient conscious cognitive processing to interact appropriately with the environment.17,18 Delaying connectedness by suppressing noradrenergic activity may be a way to prevent this. In turn, this may explain why dexmedetomidine decreased emergence delirium after volatile anesthesia, agitation in pediatric patients with sleep apnea, and delirium in the mechanically ventilated patients.19–22 To the perioperative utility of α2 agonists for mitigating pain, nausea, inflammation, and organ injury can now be added its putative effects on delaying connectedness. Translational studies building on the important preclinical findings by Kelz and others may edge us closer to improvements in clinical care by identifying other trespassing neurotransmitters in the anesthetic or sedated state, which can be modulated to improve perioperative and critical care outcomes.23

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