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The Locus Coeruleus

Site of Hypnotic Actions of α_2-Adrenoceptor Agonists?

Selective α_2-adrenoceptor agonists induce potent hypnotic effects in experimental animals and humans. As with most anesthetic agents, the anatomic site of this action has not yet been elucidated. In this issue of ANESTHESIOLOGY, Correa-Sales *et al.* provide evidence that the locus coeruleus (LC) may be an important site in mediating the hypnotic response to the α_2-adrenoceptor agonist dexmedetomidine.[1] This is in agreement with existing knowledge of the anatomy, chemistry, and physiology of the LC and may have important consequences for drug development and anesthetic practice.

The LC is a tiny brain nucleus located in the upper brainstem just under the floor of the fourth ventricle. In the human brain, it is readily identifiable because of its bluish color caused by melanin pigment. In the rat brain, it does not similarly stand out (it is not pigmented) and comprises only about 1,500 neurons. Nevertheless, the LC has become a favored target for neurobiologic investigations because of its widespread connections with other brain regions and its importance in physiologic regulation (see ref. 2).

In 1964, the LC was recognized as the major noradrenergic cell body aggregation in the rat brain (the A6 cell group of Dahlström and Fuxe[3]). In addition to norepinephrine, its cell bodies and neurites contain several other transmitter substances. Some of these transmitters mediate regulation of LC activity, whereas some subserve still undefined functions within noradrenergic neurons.[4] The LC receives afferents mainly from two rostral medullary nuclei, the *nucleus paragigantocellularis* and the *nucleus prepositus hypoglossi,* with some direct input also from surrounding gray matter areas, the hypothalamus, and the spinal cord. These centers, in turn, are regulated by a variety of converging pathways, largely autonomic in nature.[5] It has only relatively recently been discovered that the LC actually consists of more or less distinct subdivisions and several morphologically and neurochemically different cell types. Efferent projections of the LC may thus be more specialized than was previously recognized, with the various neuropeptides that are colocalized with norepinephrine possibly playing a role in this functional organization.[6] Within the brainstem, efferents from the LC project to the reticular formation and several cranial nerve nuclei; descending tracts convey fibers throughout the spinal cord; and ascending fibers are widely distributed in the forebrain, including several thalamic and hypothalamic nuclei, Meynert's nucleus, septal relay areas, hippocampus, and the cerebral cortex. The cerebellar cortex also receives noradrenergic innervation from the LC.[7]

As is appropriate for a brain center with such neurochemical and associational diversity, the LC has been linked with a variety of physiologic regulatory processes, including regulation of sleep and wakefulness, attention, orientation, learning and memory, stress, nociception, and autonomic and endocrine functions.[5] Electrophysiologic recordings from LC neurons have disclosed that spontaneous discharge rates of these cells closely correlate with the degree of arousal or vigilance of an animal, reaching their minimum during paradoxical sleep. Changes in the firing pattern of the LC have been noted to precede observable behavioral changes, leading to the suggestion that vigilance is actually controlled from this site.[8] Clearly, this would have important implications for clinical anesthetic

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practice, which uses chemical methods to manipulate human brain function.

Glutamate and acetylcholine are recognized as major excitatory neurotransmitters in the LC, and a variety of agents can inhibit its activity. γ-Aminobutyric acid and glycine (and drugs modulating their receptors) inhibit LC firing by increasing cellular chloride conductance.[9] Opioids (*via* μ-receptors) and α_2-adrenoceptor agonists, on the other hand, hyperpolarize and silence LC neurons by a different mechanism, acting on inhibitory cell membrane regulatory proteins that control inwardly rectifying potassium channels.[10]

Correa-Sales *et al.* now show that the potent α_2-adrenoceptor agonist dexmedetomidine causes a dose-dependent hypnotic response when injected locally into the LC of stereotactically cannulated awake rats.[1] This study is a logical continuation of work previously carried out in Maze's laboratory, where dexmedetomidine has been shown to exert its hypnotic–anesthetic action through central α_2-adrenoceptors coupled to a signaling pathway involving pertussis toxin –sensitive inhibitory GTP-binding proteins and hyperpolarizing potassium channels.[11,12] The present study[1] points to the LC as an important site for the hypnotic action of α_2-agonists, coalescing previously separate observations regarding the crucial role of the LC in regulation of sleep and wakefulness,[8] its high density of α_2-adrenoceptors,[13] and the potent hyperpolarizing effect of α_2-agonists in this nucleus.[10] Although previous work with clonidine had already suggested such a role for α_2-adrenoceptors in the LC,[8,14] the superior α_2-adrenoceptor selectivity and full agonist activity of dexmedetomidine make it a better pharmacologic probe than clonidine for α_2-adrenergic functions. Carefully selected pharmacologic agents and different injection sites were used in the current study to ensure the specificity of the observed effects of dexmedetomidine. The most compelling evidence of the central role of the LC in the hypnotic response is drawn from dual-cannulated rats, in which a dose of dexmedetomidine injected 2 mm lateral of the LC failed to induce sleep.[1]

Nevertheless, the relatively large doses of dexmedetomidine that were required for this effect—micrograms instead of nanograms—suggest that the search for the anatomic site(s) of α_2-agonist–mediated hypnotic actions should not quite end at this stage. The possibility remains that part of the injected dose, although given in an adequately small volume, 0.2 μl, might have diffused into the adjacent fourth ventricle and acted on other brain sites. Previous work with intracerebral injections of a much less lipophilic drug, morphine, has shown significant diffusion in brain tissue of even such small injection volumes[15]; on the other hand, that study also demonstrated that quite high local concentrations of morphine are needed to reproduce the effects induced by systemic drug administration.[15] The reasons for this discrepancy are not clear, and may be different for opioids and α_2-adrenoceptor agonists.

Alternatively, simultaneous bilateral injection of dexmedetomidine into both LCs would have revealed the true potency of the α_2-adrenergic mechanism. This suggestion is actually supported both by the current study (unilateral injection of the α_2-antagonist, atipamezole, was capable of antagonizing the hypnotic action of systemically administered dexmedetomidine),[1] and by the 10-fold potentiation of clonidine's hypnotic effects when injected bilaterally compared to unilateral administration.[14] Thus, one functional LC seems to be sufficient for the maintenance of wakefulness, a proposition supported by observations that unilateral LC stimulation is enough for an arousal response, whereas bilateral LC lesions are required for the induction of major neurophysiologic defects in experimental animals.[16]

What is the significance of the current study for clinical anesthesiology? First, it provides timely background information for the recently reported clinical properties of dexmedetomidine (*i.e.*, sedation, reduced anesthetic requirements, and hemodynamic and sympathoadrenal stabilization).[17,18] Second, it may direct future investigations aiming to exploit the full therapeutic potential of this class of agents. Molecular biologic techniques have recently confirmed the existence of three distinct α_2-adrenoceptor subtypes.[19] These isoreceptors share many common functional properties both in ligand binding and intracellular signaling, but some possibly clinically relevant differences have also been detected. Although all three subtypes are expressed in the brain, marked regional differences exist in their distributions.[20] The subtyping of the α_2-adrenoceptors of the LC has had to await the development of neurobiologic methods with sufficient specificity, sensitivity and anatomic resolution; *in situ* hybridization of subtype-specific messenger RNA should provide definitive answers in the near future.

Thus, if the LC indeed is a key site for the anesthetic actions of α_2-adrenoceptor agonists, and if these actions can be ascribed to a distinct α_2-adrenoceptor subtype, then it should become possible to develop new potent agonists targeted specifically to the pertinent receptor subtype. This would ultimately provide anesthesiologists and their patients with the beneficial effects of α_2-adrenoceptor activation (sedation, anesthetic potentiation, and possibly analgesia and cardiovascular stability),[21,22] while many of the unwanted effects (vasoconstriction and bradycardia) would, we hope, be avoided.[23]

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