Central noradrenergic neurones and the mechanism of general anaesthesia

Modern anaesthetics are, in the main, safe and predictable in their use, and highly efficient. Moreover, it could be argued that without these properties major advances in surgical practice, so often highlighted in the media, could not have taken place. However, as an example of pharmacology, the production of the anaesthetic state remains somewhat of a mystery. This mystery results from the controversies related to the existence of a unitary anaesthetic target site. From direct observation of clinical anaesthesia, this seems unlikely as different anaesthetic agents produce different ‘types’ of anaesthesia. GABA\textsubscript{A} receptors have long been held as a unifying cellular target (with some exceptions), but others have also been suggested. In this editorial, we consider the evidence in support of a role for noradrenergic transmission as a ‘wiring’ target for anaesthetic action. The clear role of this system in analgesia is not considered.

Norepinephrine is a major central nervous system neurotransmitter in the brainstem. Noradrenergic neurones are of great importance in the regulation of a range of behaviours including the sleep–wake cycle, feeding, thermoregulation, attention, motor activity, and growth and development.\textsuperscript{1} In addition, there are many studies suggesting that noradrenergic system(s) may be involved in the production of the ‘anaesthetic state’. In the brain, the A1, A2, A5, and A7 noradrenergic clusters constituting the lateral tegmental area, project to the thalamus and hypothalamus.\textsuperscript{2} The locus coeruleus (A6 cluster), which is distinct from the lateral tegmental area, innervates the cerebral cortex, hippocampus, cerebellum, and spinal cord.\textsuperscript{2}

The activity of locus coeruleus neurones is slow and regular during wakefulness.\textsuperscript{3} In contrast, when an animal becomes drowsy, entering slow wave and then REM sleep, there is a decrease in discharge rate such that during REM sleep these neurones are silent.\textsuperscript{3} Interestingly, all noradrenergic projections to the cerebrocortex originate from the locus coeruleus.\textsuperscript{3}

The preoptic area receives input from both the locus coeruleus (A6), and the lateral tegmental group (A1, A2, A5, and A7) noradrenergic neurones.\textsuperscript{4} In addition, neurones in the preoptic area project back to the locus coeruleus.\textsuperscript{5} This area plays an important role in sleep or hypnosis. What is the role of noradrenergic neurones in this area? Most of the previous studies\textsuperscript{6} suggest that norepinephrine neurones in the preoptic area may contribute to wakefulness, as direct activation or injection of norepinephrine into this area inhibits sleep. However, several studies also suggest that some norepinephrine neurones may be involved in the induction of sleep.\textsuperscript{7,8} Mohan Kumar and colleagues\textsuperscript{7} reported that microinjection of norepinephrine into the medial preoptic area after destruction of the ventral noradrenergic bundle induced sleep. This group also reported that there was a mild reduction in sleep and an increase in wakefulness after destruction of catecholaminergic terminals at the medial preoptic area by bilateral intracerebral injection of 6-hydroxydopamine.\textsuperscript{8} Thus, it appears that noradrenergic fibres in the medial preoptic area may be hypnogenic.

Central noradrenergic neurones are regulated by both \(\alpha\)- and \(\beta\)-adrenergic receptors. It has been reported that the \(\alpha_1\)-adrenoceptor antagonist prazosin, given orally, increased active waking and slow wave sleep and decreased paradoxical sleep in the rat.\textsuperscript{9} In contrast, \(\alpha_1\)-adrenoceptor stimulation with systemic methoxamine, increased aroused wakefulness and decreased slow wave sleep and paradoxical sleep in cats.\textsuperscript{10} In addition, prazosin increased but the \(\alpha_1\)-agonist ST 587 decreased the duration of thiopental anaesthesia in rats.\textsuperscript{11} Matsumoto and colleagues also reported that direct intracerebroventricular administration of methoxamine dose-dependently reduced pentobarbital anaesthesia time in mice.\textsuperscript{12} Most of the central physiological effects of \(\alpha_2\)-agonists can be attributed to \(\alpha_2\)-adrenoceptors present in the locus coeruleus.\textsuperscript{13} In rats, microinjection of the \(\alpha_2\)-agonist dexmedetomedine into the locus coeruleus \textit{per se} produces anaesthesia (defined as a loss of righting reflex).\textsuperscript{14} \(\alpha_2\)-Agonists also reduce anaesthetic requirement in human and many other species.\textsuperscript{15} In contrast to these data, the \(\alpha_2\)-antagonist yohimbine decreases sleep,\textsuperscript{16} and anaesthesia time\textsuperscript{15} in a variety of non-human species.

The Angel group showed that propranolol, a non-selective \(\beta\)-antagonist, dose-dependently increased sleep time\textsuperscript{16} and thiopental anaesthesia time\textsuperscript{11} in rats. However, they failed to show an effect with the selective \(\beta_1\)-antagonists metoprolol and atenolol.\textsuperscript{11,17} They also studied the role of \(\beta_2\)-adrenoceptors in sleep and general anaesthesia,\textsuperscript{11,16,17} and found that the selective \(\beta_2\)-antagonist ICI
118551 increased sleep time and the duration of thiopental anaesthesia. Collectively, these data indicate that the effects of the non-selective antagonist, propranolol, may be mediated via $\beta_2$-adrenoceptors.

The recently identified (from rat hypothalamus) neuropeptides orexin A and B are endogenous agonists for the G-protein-coupled orexin-1 (OX1) and OX2 receptors. Orexin A has equal affinity for OX1 and OX2, while orexin B has a higher affinity for OX2. Orexins and their receptors are widely distributed in the brain. Orexins activate the locus coeruleus noradrenergic system and this activation may increase arousal and locomotor activity. In addition, several reports suggest a link between orexin receptors and narcolepsy. Therefore, modulation of noradrenergic neurones by orexins and their receptors may contribute to control of the sleep–wake cycle. Moreover, we suggest that these neuropeptides and their receptors may also be involved in general anaesthesia, although this remains to be examined.

Based on these considerations, we and others have begun a systematic evaluation of a range of anaesthetic agents on central norepinephrine release using in vivo microdialysis techniques. Mizuno and colleagues reported that intraperitoneal pentobarbital inhibited norepinephrine release from the medial preoptic area in rats. In addition, we have shown that systemic administration of midazolam and propofol significantly reduced norepinephrine release from the medial prefrontal cortex, but pentobarbital was ineffective. As noradrenergic neurones in the prefrontal cortex receive innervation from the locus coeruleus, the activity of noradrenergic neurones in the prefrontal cortex indirectly reflects locus coeruleus activity. Thus, anaesthetics that activate or enhance GABA$_A$ receptors may reduce noradrenergic neuronal activity. In contrast, ketamine, nitrous oxide and xenon, which have NMDA receptor antagonistic actions, markedly increased norepinephrine release from the prefrontal cortex and preoptic area in rats. Clearly, anaesthetic modulation of norepinephrine release depends on the type of anaesthetic. This might argue against noradrenergic transmission as an anaesthetic target. However, as we have already mentioned, a unitary site is highly unlikely. Loss of consciousness results not only from a reduction in cerebral activity, but also as a result of cerebral excitation such as occurs during convulsions. In addition, sleepiness is induced by not only hypothermia but also by increased body temperature that activates heat-sensitive neurones in the preoptic area. We feel that wakefulness may occur over a set range and that when this range is exceeded (above or below), unconsciousness may occur. In support of this hypothesis we found that physostigmine, which has been reported to antagonize ketamine anaesthesia, reduced both the duration of ketamine anaesthesia and ketamine-increased norepinephrine release from the rat prefrontal cortex.

Collectively, the data presented in this editorial provide compelling evidence in favour of a role for noradrenergic transmission in both the control of wakefulness and the production of the ‘mysterious’ anaesthetic state.

K. Hirota
T. Kushikata
Department of Anesthesiology
University of Hirosaki School of Medicine
Hirosaki 036-8563
Japan

References
3 Berridge CW, Abercrombie ED. Relationship between locus coeruleus discharge rates and rates of norepinephrine release within neocortex as assessed by in vivo microdialysis. Neuroscience 1999; 93: 1263–70
8 Ramesh V, Mohan Kumar V. Changes in sleep-wakefulness after 6-hydroxydopamine lesion of the preoptic area. Neuroscience 2000; 98: 549–53
14 Nacif Coelho C, Correa Sales C, Chang LL, Maze M. Perturbation of ion channel conductance alters the hypnotic response to the $\alpha_2$-adrenergic agonist dexmedetomidine in the locus coeruleus of the rat. Anesthesiology 1994; 81: 1527–34

812
16 Angel A, Majeed AB. Alterations of ‘sleeping time’ in the rat induced by drugs which modulate central monoaminergic systems. *Br J Anaesth* 1990; 64: 594–600