What can *in vivo* electrophysiology in animal models tell us about mechanisms of anaesthesia?

C. Vahle-Hinz[1]* and O. Detsch[2]

[1]*Institut für Physiologie, Universitätsklinikum Hamburg-Eppendorf, D-20246 Hamburg, Germany.*
[2]*Klinik für Anaesthesiologie, Technische Universität München, D-81675 München, Germany*
**Corresponding author*

Br J Anaesth 2002; **89**: 123–42

Keywords: anaesthesia, mechanisms; analgesia; anaesthetics volatile; anaesthetics i.v.; brain, brain stem; brain, reticular formation; brain, thalamus; brain, somatosensory cortex; brain, $GABA_A$ receptor; spinal cord, sensory block

The search for the mechanisms of anaesthesia has resulted in an overwhelming multitude of cellular and subcellular sites identified as potential targets of anaesthetic action. Attempts to define a unitary mechanism of action for the diverse types of chemicals with anaesthetic potency have failed, and it is now recognized that agent-specific effects on defined neuronal sites, including the constituents of synaptic transmission, may underlie their actions. The next step in answering the question 'how do anaesthetics cause anaesthesia?' is to associate these cellular mechanisms of action—most of which were described using *in vitro* experiments—with areas and neuronal networks within the nervous system ('where do anaesthetics cause anaesthesia?') using preparations with fully intact pathways. Combining the knowledge gained from *in vitro* experiments with clinical experience, animal experiments can be designed to take the questions about anaesthetic actions to the level of the living organism. This approach is important, as it is controversial which of the many effects of anaesthetics demonstrated *in vitro* are important for producing relevant *in vivo* effects, such as hypnosis, amnesia, analgesia/antinociception, and the suppression of movement in response to noxious stimulation.[44 114]

The production of unconsciousness (hypnosis) and inhibition of memory formation (amnesia) require effects on cortical function;[118 120] on the other hand, the suppression of motor and autonomic responses to noxious stimuli and the inhibition of sensory processing may well occur at subcortical sites. Many anaesthetic agents, in clinically used doses, can produce several components of anaesthesia, but they typically show a profile of preferred actions. Moreover, neurotransmitter receptors and other putative neuronal targets of anaesthetics (such as voltage-gated or background ion channels) have a distinct distribution and density in the central nervous system (CNS). For example, the $GABA_A$ receptors in different regions of the CNS are composed of varying combinations of subunits which differ in their sensitivity to anaesthetics.[88] Therefore, anaesthetics may preferentially affect certain regions of the CNS and may show, for example, a 'top-down' or 'bottom-up' effectiveness with increasing dose within the hierarchically organized neural systems.

This review will focus on *in vivo* animal studies recording neuronal activity in the peripheral nervous system (PNS) and CNS involved in the different aspects of the anaesthetic state induced by general anaesthetics. We discuss a selection of studies undertaken with this aim, but further data can be hidden especially in electrophysiological investigations on CNS functioning, where the anaesthesia of the experimental animal is a necessary but not central issue. A common end point for studies on anaesthetic mechanisms is the withdrawal response to noxious stimulation, which comprises a motor and a sensory component and some information processing with all three readily assessable in electrophysiological recordings. The suppression of sensory perception is accessible for study in animal models; the site within the ascending sensory pathways and the neuronal networks affected by anaesthetics and their targets among the constituents of synaptic transmission can be explored. As suppression of pain is one of the major goals of anaesthesia and, indeed, most *in vivo* studies on the mechanisms of anaesthesia address questions about processing of pain and touch, this review will focus on the somatosensory system (see Fig. 1). There are few studies on suppression of hearing, another interesting aspect of anaesthesia in the operating room. Hypnosis and amnesia are

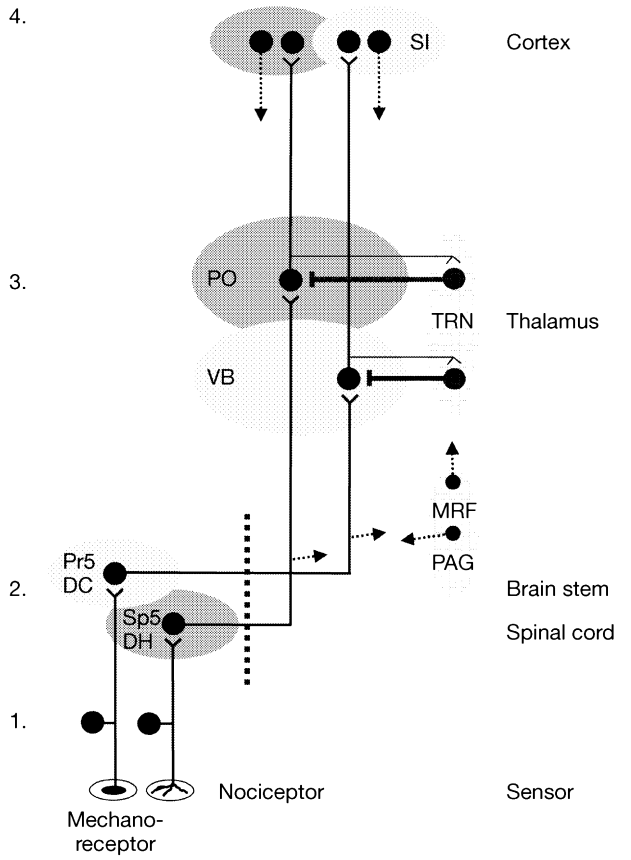

Fig 1 Schematic diagram of the major pathways of the rat's somatosensory system transmitting information about touch from mechanoreceptors and information about painful stimuli from nociceptors to the primary somatosensory cortex (SI). Mechanoreceptive signals ascend to the dorsal column nuclei (DC, extracranial system) or principal trigeminal nucleus (Pr5, cranial system) and travel to the contralateral VB complex; the midline is represented by a dotted line. Nociceptive signals ascend to the dorsal horn (DH, extracranial system) or spinal trigeminal nucleus (Sp5, cranial system) and reach the PO complex on the contralateral side. Modulatory influence on these pathways is exerted by descending bulbospinal projections, for example, the PAG and MRF, and from thalamic (TRN) and cortical regions.

difficult to assess in animal models and are not covered in this review.

Assets and drawbacks of *in vivo* electrophysiology

Recording methods

Methods used in *in vivo* animal studies on neuronal activity are: (1) evoked potential recordings of peripheral nerves, central fibre tracts or nuclei, and cortical areas; (2) extracellular single neurone recordings of action potential (spike) discharges which reflect the excitability of the neurone above its firing threshold; and (3) intracellular recordings of postsynaptic potentials and action potentials. The two questions, the 'where?' and the 'how?' of anaesthetic action may be answered to a varying extent with these methods. From latency measurements of evoked potentials, whether elicited by electrical or natural stimulation, the regions involved within the hierarchically organized systems of the CNS can be detected; electrical stimulation procedures can differentiate the fibre types involved in the PNS and to a certain degree also in the CNS; and stimuli such as non-noxious mechanical or noxious laser-heat stimuli can discriminate between sensory modalities. Evoked potentials of the CNS originate from a large population of neurones and reflect postsynaptic, rather than spike, events. Hence, they reflect a gross average of the net population activity, obscuring differential functions within the network. Therefore, details of the transmission and processing of stimulus information necessary for sensory perception of, for example, intensity, quality, duration, and velocity, cannot be assessed.

Extracellular single neurone recordings, in contrast, are ideally suited to provide this kind of information. Several caveats, however, have to be considered. (1) To infer from one neurone to the population within the system requires data from larger numbers collected sequentially or simultaneously from multi-electrode arrays. (2) An electrode introduced into a CNS nucleus picks up action potentials from different parts of a neurone: the soma and dendritic branches, and the axon. Axons found within a nucleus typically may originate from three sources: ascending and descending input fibres and fibres from the neurones of the nucleus itself, traversing it *en route* to their termination fields. Soma and fibre recordings can be distinguished electrophysiologically by their form and duration. The sources of fibres can be identified by orthodromic and antidromic electrical stimulation. (3) Two types of neurones usually comprise a CNS nucleus: neurones projecting to one or several other brain regions and interneurones making connections within the nuclear boundaries. Projection neurones can be positively identified by electrophysiological means (antidromic activation from the site of their axonal projection), interneurones cannot. In the spinal dorsal horn the situation is particularly complex, as not only neurones belonging to different ascending and descending systems occur in close proximity or may even feed into several systems, but also those mediating different modalities/submodalities (touch, proprioception, viscerception, pain). Within the somatosensory system, low-threshold mechanoreceptive (LTM), wide dynamic range (WDR), and high-threshold (HT), that is nociceptive-specific, neurones may occur intermingled also at higher CNS stages (for definition of neuronal classes, see below). These, however, can be identified by use of stimuli known to activate adequately the sensory receptors within their peripheral receptive field (RF) (see also Fig. 2). Even more complicated than in the 'specific' sensory CNS areas, is the situation in the 'non-specific' areas, that is modulatory regions such as, for example, the brain stem reticular

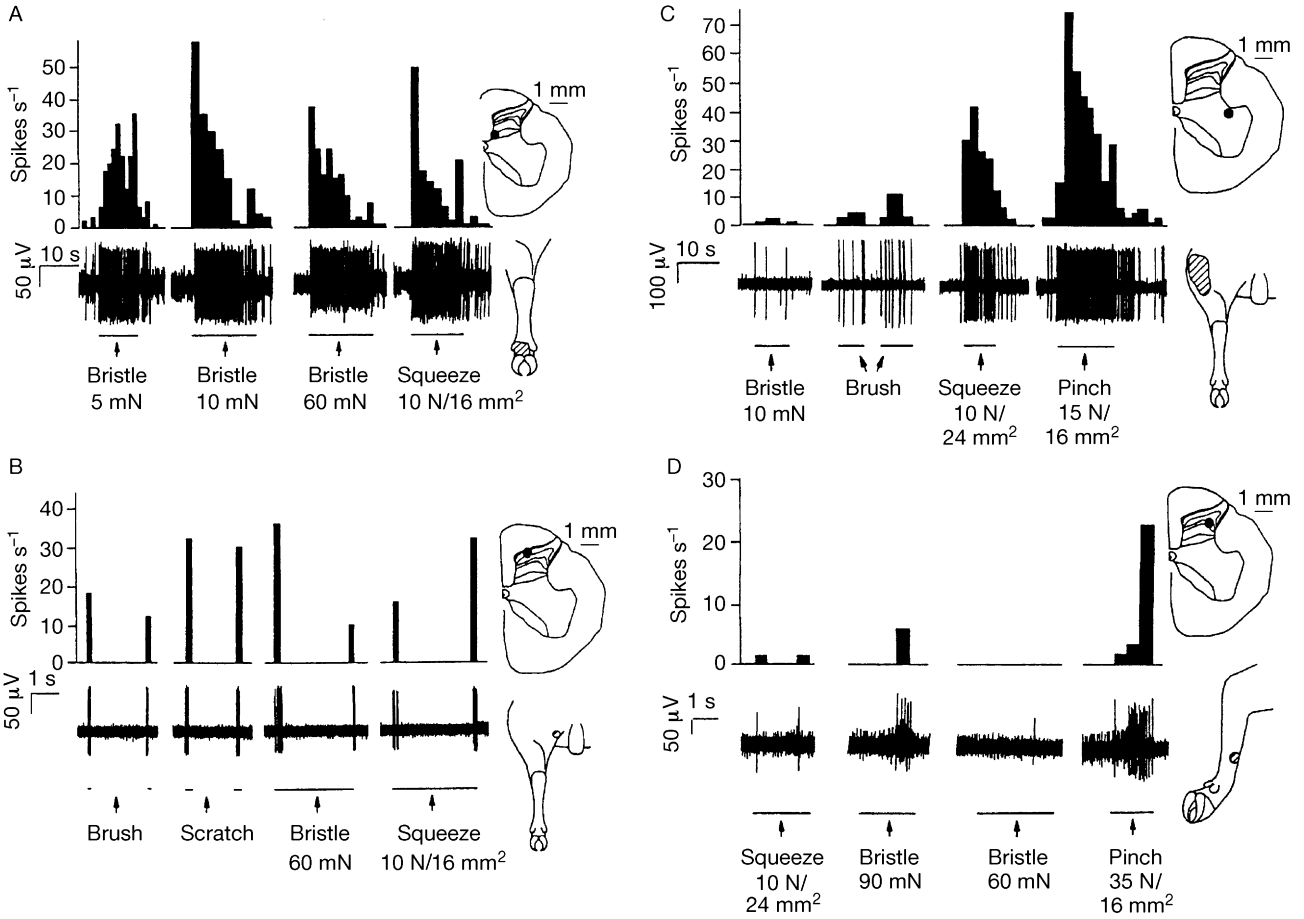

Fig 2 Characteristics of LTM, WDR, and nociceptive-specific (NS) neurones recorded in the spinal cord of awake sheep. The original spike records and the histograms of the spike-firing rate show how stimulus intensity is encoded in the spike rate. (A) The LTM tonic neurone responds continuously during stimulus presentation and in a graded manner to increasing intensities of innocuous mechanical stimulation with von Frey hairs (5 and 10 mN), whereas with 60 mN and noxious squeeze no further increase in discharge rate is induced. (B) The LTM phasic neurone responds with on/off discharges to stimulus presentation. (C) The WDR neurone shows graded responses to non-noxious (10 mN von Frey hair, brush, squeeze) and noxious intensities (pinch) of mechanical stimuli. The noxious pinch stimulus elicited a withdrawal reflex. (D) The HT or nociceptive-specific neurone was consistently activated only by the noxious pinch stimulus that induced a withdrawal reflex. Insets show the location of the neurones in the spinal cord and the size of their RFs on the sheep's hind limb (from[56]).

formation or cortical association areas, where the association between neuronal activity and experimental stimuli is not always clearly discernible (see below). These cortical regions, however, are considered to be the sites responsible for conscious perception and hence those most interesting to study in the context of mechanisms of anaesthesia.

Apart from certain neurosurgical procedures, single neurone recordings in humans are difficult to obtain and obviously not suitable for systematic study.[71 112] Studies in humans using recordings of gross neuronal signalling activity (EEG and MEG) or imaging techniques which are based on cerebral metabolic (CMR) or blood flow (CBF) changes associated with neuronal function (fMRI, SPECT, PET) have highlighted brain areas involved in anaesthesia, that is the 'where?' of anaesthetic action. An implicit but pivotal assumption for this type of imaging study, and for many *in vivo* electrophysiological studies in animals, is that an anaesthetic-induced change in neuronal activity (as measured by neuronal activity or CBF/CMR change) results from the local effect of the drug at the site where the measurement is taken. This, however, is not necessarily so: on the contrary, the effects measured may reflect anaesthetic action at a quite distant site.[76] For example, an anaesthetic-induced decrease in cortical activity may result from suppression of the transfer of information at cortical, thalamic, brain stem, spinal, and/or peripheral sites. The ideal method, therefore, would be to record neuronal activity simultaneously at all of these sites; an approach hindered among other things, when natural stimulation is used by the requirement to match RFs. An approach to investigate the spinal actions of anaesthetics is to isolate the spinal cord by proximal spinal cooling, transection, or decerebration; these manoeuvres, however, may produce their own alterations (see below). An elegant method to

circumvent the difficulty to pinpoint the site of anaesthetic action is to record from a single neurone and, simultaneously, locally administer drugs to the neurone's vicinity (using microiontophoresis or picoejection) that activate or inhibit membrane receptors/channels. This method in addition provides information about the 'how?' of anaesthetic action.

Nearly all anaesthetics and agonists/antagonists at their potential targets (such as presynaptic and postsynaptic neurotransmitter receptors, ion channels, or uptake mechanisms) can be administered by microiontophoresis or picoejection. The pitfalls of these techniques, for example, unspecific neuronal excitation by current, pH, or high doses of ejected drugs, have to be controlled carefully. The dose of the ejected drug is difficult to determine as it depends on the time and current of application or the ejection pressure, the duration, and frequency of the pulses. Furthermore, the dose depends on the distance and geometry of the pipette tips with respect to the recorded neurone, the diffusion within the tissue and the uptake or metabolic mechanisms present; thus, the dose has to be adapted to each individual recording situation. Quantification of the effects of ejected drugs, therefore, warrants careful interpretation.[59 73] Intracellular recordings address the 'how?' in even more detail; however, *in vivo* the recording time is limited and usually cannot be extended to the several hours necessary to permit repeated systematic changes in experimental conditions.

In single neurone recordings the traditional measure taken is the action potential discharge rate (expressed as impulses or spikes or events per unit of time). In studies using experimental stimuli, a distinction is made between the ongoing ('spontaneous') activity, that is the discharge activity in the absence of experimental stimulation, and the response activity evoked by electrical stimulation of afferent inputs or 'natural' stimulation of the RF of the neurone using stimuli adequate for the sensory modality under study (see Fig. 2). Normally, the response rate is determined by stimulation of the centre of the RF, which is the peripheral area from which the highest response rate can be elicited. Another measure of response activity is the size of the RF, which is determined by mapping the boundaries of the RF area. RFs of CNS neurones may be larger or smaller than those of primary afferents because of convergence and differential organization of centre/surround areas. The discharge pattern, such as tonic or burst firing, or afterdischarges, is also considered to hold important information. In contrast to stimulus-evoked response discharges, the biological significance of the ongoing activity is not readily discernible under most experimental conditions. Many attempts based on sophisticated mathematics have been applied to decipher these spike train patterns.[49 91 120 125] The question remains whether changes in discharge rate adequately reflect the neuronal processes underlying the anaesthetic-induced suppression of sensory perception, hypnosis, and amnesia.

Animal models

The effects of anaesthetics have been studied in animal models using a background anaesthetic for 'baseline' recordings followed either by the administration of another anaesthetic or higher doses of the initial anaesthetic; with this preparation, the production of anaesthesia *per se* cannot be studied. The need for a reliable drug-free baseline has resulted in the use of decerebrate animal models that limit experiments mostly to studies on spinal cord mechanisms. As the gross surgical intervention of decerebration again results in an unphysiological state (for further discussion, see below), chronic preparations have been established where rats, cats, and monkeys were trained to accept a recording and stimulation session while being restrained. Again, training and the experimental situation might impact on the results. Recently, models of unrestrained animals have been developed, which, in turn, suffer from problems of inconsistent stimulus presentations.

While the possibility to compare the activity of individual neurones in the awake and anaesthetized animal is appealing, to maintain a recording from the same neurone under both conditions is technically challenging; therefore, some authors prefer the comparison of the activity between two sets of neurones, one 'awake' and one 'anaesthetized'. Furthermore, the 'awake' condition does not necessarily reflect a uniform state of neuronal activity, but it is subject to shifts in arousal and attention (e.g.[42 82]).

Apart from different preparations, a reason for incongruent results in animal studies may be species differences. Furthermore, translating results from animals to the situation in humans may suffer from similar constraints.

Somatosensory system

The somatosensory system comprises touch and pain modalities. Figure 1 shows a simplified diagram of the major pathways. The peripheral sensors in the skin, muscles, joints, and internal organs are terminals of Aβ-fibres and classified as LTM (SA, RA, and PC); terminals of Aδ- and C-fibres constitute the nociceptors. Tactile events are encoded in trains of action potentials that contain information about stimulus features (intensity, duration, velocity, and location on the body surface). Nociceptors of the skin are activated by mechanical, thermal, or chemical noxious stimuli, which are those damaging or threatening to damage the integrity of the body surface. Nociceptive and tactile information from the body periphery is conveyed via the spinal cord (dorsal horn, extracranial areas; spinal trigeminal nucleus, cranial areas) and brain stem (dorsal column nuclei; principal trigeminal nucleus), respectively, to the posterior (PO) and ventrobasal (VB) complexes of the thalamus and further on to the primary somatosensory cortex. Throughout the ascending pathways, the body surface is represented in somatotopic order.

These lateral thalamic and cortical areas are the targets of the sensory-discriminative aspects of pain, whereas the motivational-affective aspect of pain is mediated in medial regions, mostly via the brain stem reticular formation and medial thalamic nuclei. Primary and secondary sensory cortices receive inputs from the lateral system, while the medial system projects to other cortical regions—for example, the cingulate gyrus, or the prefrontal cortex. Information is not merely relayed in the different stages of the ascending pathways, but processed by local networks involving intrinsic interneurones and modulated by descending connections from the cortex, and from thalamic and brain stem regions for which the thalamic reticular nucleus (TRN), the mesencephalic reticular formation (MRF), and the periaqueductal grey (PAG) are shown as examples in Figure 1.

Peripheral nervous system

In vivo studies on the effects of general anaesthetics on sensory receptors or peripheral nerve fibres are sparse. Axonal conduction of action potentials, even in fine unmyelinated nerve fibres, appears largely to be unaltered by anaesthetics as much higher (supraclinical) concentrations of anaesthetics are necessary to produce any effect compared with those altering synaptic transmission (for review see[95 96]).[15 69] As early as 1967, de Jong and Nace[32] studied the effects of ether, methoxyflurane, halothane, and nitrous oxide on the compound action potential of the saphenous branch after electrical stimulation of the femoral nerve, and on action potential responses to mechanical stimulation of the nerve fibres' cutaneous RFs. They used concentrations up to ranges where the EEG and/or the arterial pressure were profoundly depressed. The only significant change seen was a small increase of the C-wave under ether. Intravenously administered pentobarbital had no effect. They concluded from their study that volatile anaesthetics in usual anaesthetic concentrations have no important effect on conduction in the peripheral nerve or on generation of impulses in cutaneous receptors. Correspondingly, the tuning curves of auditory nerve fibres in the gecko were best (lowest thresholds, highest discharge rates) under pentobarbital and decreased only with high doses of isoflurane or ketamine.[40] Using intracellular recordings, Puil and Gimbarzevsky[94] studied anaesthetic effects on membrane potentials and electrical properties of trigeminal root ganglion neurones in decerebrate guinea pigs. In more than two-thirds of the neurones, isoflurane (2–3% for 0.5–3 min) caused no consistent alterations of electrical neuronal properties; in the remaining neurones, isoflurane (2–4%) modestly reduced neuronal excitability as reflected in a reduction in spike electrogenesis and repetitive firing. In contrast, nitrous oxide had predominantly excitatory effects with increased repetitive firing.

Some anaesthetics, however, seem to cause sensitization of cutaneous nociceptors innervated by Aδ- and C-fibres. This was demonstrated for halothane (0.8%)/nitrous oxide (67%) as opposed to barbiturate anaesthesia in monkeys.[18] It is interesting to note that the threshold to heat stimuli decreased and the responses increased (2-fold for C-fibre afferents; 5-fold for A-fibre afferents), whereas no changes to innocuous mechanical stimulation were seen in these mechanosensitive and heat-sensitive fibres. This implies a differential effect of halothane on the different types of transduction mechanisms recently shown to underlie heat and mechanical nociceptors.[20] A similar excitatory effect of halothane, isoflurane, and enflurane was demonstrated for C-fibres in an *in vitro* rabbit corneal preparation.[74] However, these excitatory effects on peripheral nociceptors cannot account for the suppressive effects of volatile anaesthetics on CNS neurones. This is also supported by a study in dogs,[8] where the authors determined the minimum alveolar concentration (MAC) of isoflurane (as tested with noxious stimulation at the tail), and showed that MAC is independent of peripheral isoflurane effects when isolated perfusion of hind limbs and tail was used to allow the selective reduction of isoflurane concentration.

Spinal cord

At the level of the spinal cord, two systems are of interest: the ventral horn with the motor neurones as the output side of motor reflexes and the dorsal horn with sensory neurones feeding into the motor reflexes and into the ascending sensory pathways. Somatosensory neurones are classified as LTM, WDR, and HT or NS (nociceptive-specific). LTM neurones respond maximally to low-threshold (innocuous) mechanical stimulation of their RF (light touch, pressure, hair movement, or vibration) without an increase with stimuli reaching the HT (noxious) range (Fig. 2A and B; see also Fig. 4). WDR neurones receive both low- and high-threshold input and thus respond with increasing discharges to mechanical stimuli from the innocuous to the noxious range (Fig. 2C). In addition to the mechanosensitivity, many of the WDR neurones also respond to noxious thermal stimuli and receive convergent input from muscle and viscera. HT neurones are activated only by stimuli of noxious strength (Fig. 2D).

Studies on the mechanisms of suppression of pain-evoked movements have shown that the spinal cord contributes significantly (for review see[28]). Volatile anaesthetics, barbiturates, nitrous oxide, and propofol depress reflex activity (nocifensive movements) by both suppression of the excitability of spinal motor neurones and by suppression of responses of spinal nociceptive neurones in rats, cats, and monkeys (Fig. 3).[28 84] The effects are dose-dependent and appeared to be largely independent of supraspinal actions, as has been demonstrated by the block of the descending modulatory influences through transection or reversible cooling of the spinal cord, or in decerebrate animals.[33–36 68 124] Also, differential lamina-specific anaesthetic effects have been described in the dorsal horn.[68] A

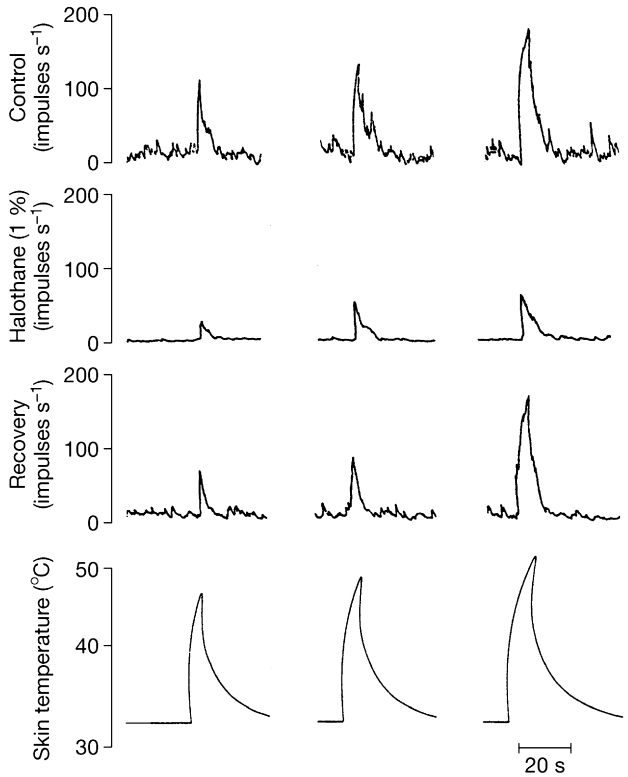

Fig 3 Graded responses to noxious-heat stimuli of a dorsal horn WDR neurone and the effects of halothane on neuronal discharge activity. The responses and the ongoing activity are reversibly reduced by 1% halothane. Note that the responses are reduced but not obliterated. As the recordings were made in decerebrate, spinal cord-transected cats, the results show that the halothane effects are not caused by indirect supraspinal actions. Polygraph tracings of the discharge rates (from[84]).

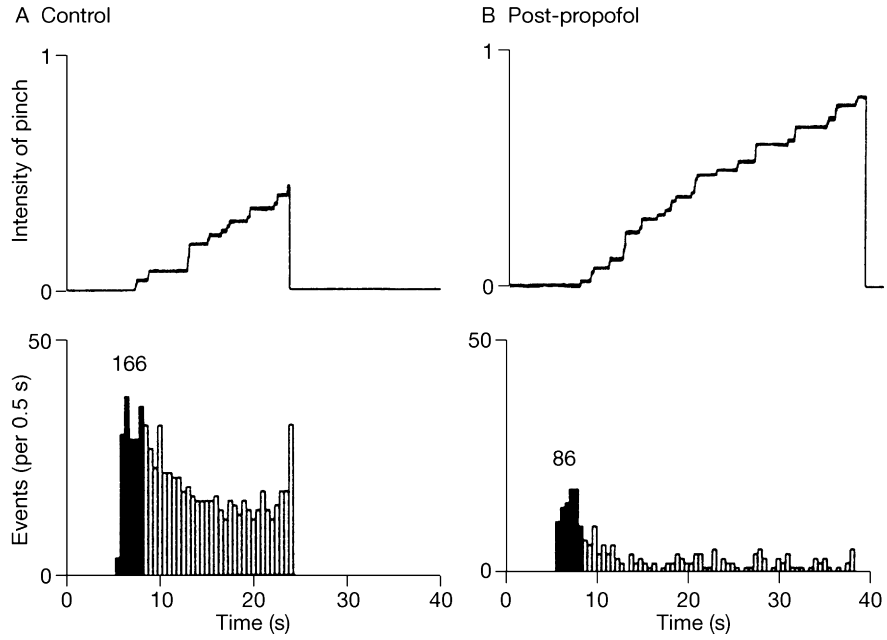

Fig 4 Reduction of the response of a LTM dorsal horn neurone by propofol. Responses are compared between the physiologically intact drug-free awake state (A) and the anaesthetized state in a cat (B, 8 min after bolus injection of propofol). Although the increasing stimulus pressure reaches the noxious range (the animal showed the first sign of the reflex withdrawal at the end of the stimulus) the response does not increase as is typical for LTM type neurones; this is shown also for the anaesthetized condition, demonstrating the preserved tonic response pattern while the response magnitude decreases (reduction to 50% of the initial response during touching the skin before pressure is increased; black bars) (from[113]).

different approach was taken in a preparation (goat model) where the circulation and hence anaesthetic supply to the brain and to the spinal cord was separated.[7] In this model propofol and thiopental had a direct depressant effect on nociceptive responses of dorsal horn neurones, while administration of propofol or thiopental to the cranial circulation (hence to the brain) had no effect.[12 110]

The suppression of nociceptive sensory transmission by general anaesthetics is similar to the effects of opioids administered to the spinal cord (e.g.[60 67 111 123]). Ketamine seems to play a special role, also evident from a selective depressant effect on dorsal horn nociceptive neurones as opposed to LTM neurones.[29 113] However, Cairns and colleagues[17] have shown that ketamine may have a short-acting effect on LTM neurones in the trigeminal nucleus.

With the availability of animal models using awake rats, cats, or monkeys it became possible to compare the activity of dorsal horn cells in the drug-free situation with that during administration of anaesthetics.[16 25 75] Because of the constraints on using noxious stimuli in awake animals while recording from spinal cord neurones, the focus shifted to LTM neurones and therefore towards ascending sensory processing instead of studies on spinal mechanisms of nociception. In most studies, anaesthesia-induced reduction of low-threshold RF sizes (by about 50%) and LTM response rates were demonstrated, while similar changes were shown for (the few) WDR neurones, and no nociceptive-specific neurones were tested.[66 89 113] This was shown for propofol (Fig. 4), while ketamine had no effect[113] and RFs increased during REM sleep.[66] Halothane again induced reduction of RF sizes and responses to brushing the RF or application of continuous pressure (tonic response).[89] Although no data were presented, it was noted that responses to slowly adapting input appeared more susceptible to halothane than responses to rapidly adapting input. On the other hand, 2.1% enflurane increased LTM responsiveness to almost 200%, while RF size was reduced.[126] Interestingly, in the same study it was found that WDR responses to innocuous stimulation increased with enflurane, while responses to noxious stimuli were reduced to approximately 50%.

In contrast to these studies in rats and cats, in a chronic sheep model (Fig. 5) RF sizes were significantly larger under halothane (1.5–2.5%) for WDR, LTM, and NS neurones, but ongoing activity was not affected.[56 57] The increase in RF size was assumed to be probably because of a dampening of the descending inhibitory control by halothane. Von Frey mechanical threshold was higher only for WDR neurones. Although populations rather than individual neurones were compared, the results are validated by a large number of neurones studied in both the dorsal and ventral horns. The conflicting results from the awake sheep model[56] compared with rat or cat models[33 35 89 124 126] pose interesting questions; apart from the species differences, effects of training the animals to sit quietly during the recording session, or the effects of the

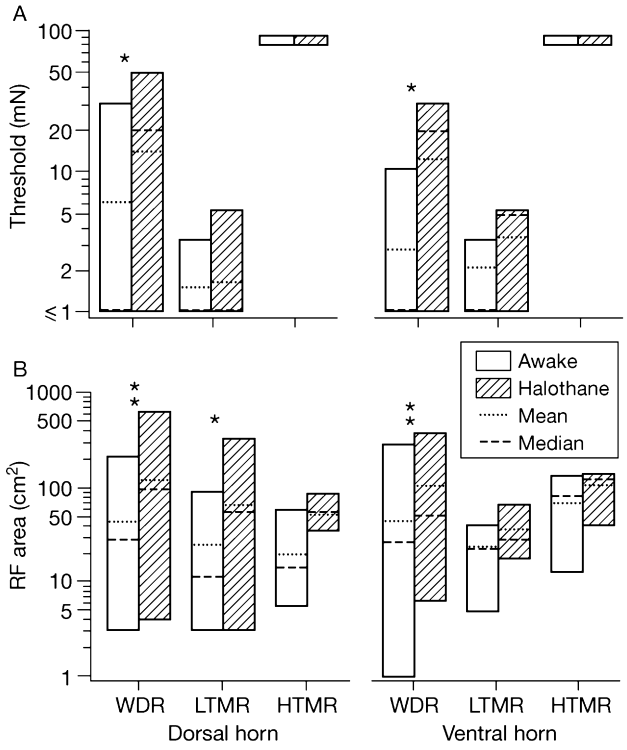

Fig 5 Mechanical response thresholds (A) and RF areas (B) of LTM, WDR, and NS neurones recorded in the spinal cord. Range, mean, and median values are given for WDR, LTMR, and HTMR (i.e. NS) neuronal classes recorded in the awake and halothane anaesthetized sheep. The RF area increases during halothane anaesthesia in WDR and LTM neurones, in WDR neurones also the response threshold increases. *, **Significant differences between awake and halothane groups ($P<0.05$ and $P<0.01$, respectively) (from[56]).

acute spinalization/decerebration, that is, removal of descending inhibition, might play a role. Spinal neuronal responsiveness is altered in a time-dependent manner when descending modulatory controls are removed,[9 53 62 122] resulting, for example, in overexcited neurones (as seen in high ongoing activities). Cutaneous RFs are controlled by descending influences and spinal section usually causes expansion of RFs,[43 119] although reduction of RFs may also result.[124]

Another way to pinpoint anaesthetic action to a specific site is the experimental testing of neurotransmitter receptors known to be affected by the drugs from *in vitro* studies. There are only a few studies of this type. The halothane-induced reduction of RF size was reversed 50% by intravenously administered picrotoxin, while it had no effect on the brush response.[89] The suppressive effects of propofol (measured with tail-flick latency) within the spinal cord involve $GABA_A$ receptors as demonstrated by intrathecal administration of the $GABA_A$ antagonist bicuculline.[83] In addition, spinal δ-opioid receptors may be activated indirectly. A more direct study on presynaptic and postsynaptic sites of action of anaesthetics was done by Galindo[46] using the cuneate nucleus of decerebrate cats.

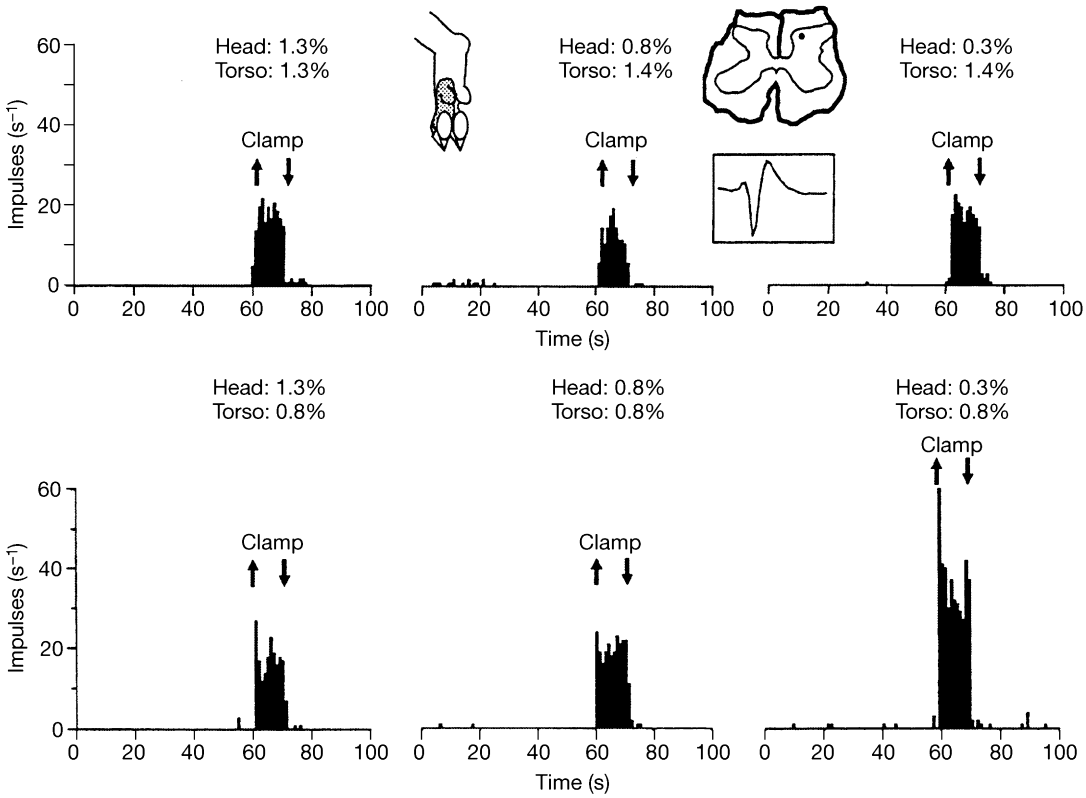

Fig 6 Nociceptive responses of a dorsal horn neurone increases with decreasing cranial (head) isoflurane concentration under low torso (hence spinal cord) isoflurane concentration (bottom row) but not under high torso concentration (top row). Responses of a WDR dorsal horn neurone (inset shows recording site) to a standard noxious mechanical clamp stimulus applied to the RF on the goat's hoof (inset). Spike histograms (bin width 1 s) (from[62]).

Through careful electrophysiological identification of the neuronal elements (relay and interneurones, responsiveness to skin, hair, or joint stimulation) and local administration of the anaesthetics and of glutamate and GABA by iontophoresis from multi-barrel pipettes, differences in the mechanisms of the depressant action of a local anaesthetic (procaine), a barbiturate (pentobarbital), and a volatile anaesthetic (halothane) were dissected. Procaine was found to have a non-specific depressant effect on presynaptic and postsynaptic elements, while pentobarbital specifically suppressed postsynaptic excitation and halothane enhanced synaptic inhibition, that is the effect of locally administered GABA.

Facilitatory effects have been shown for low concentrations of inhaled anaesthetics that may induce hyperalgesia (paw withdrawal to heat[127]), similar to barbiturates which unmask nociceptive properties in spinal cord neurones.[26 27 61] Facilitation of synaptic transmission through dorsal column nuclei has been demonstrated in the decerebrate cat to result presumably from enhanced release of transmitter under halothane, ketamine, methohexital, and pentobarbital.[80]

The spinal cord dorsal horn has been shown in many studies to be the major site of action of anaesthetics for the suppression of purposeful movements in response to noxious stimuli. When a small range of isoflurane concentration on either side of the MAC was used, however, variable but minimal depressant effects on responses of dorsal horn cells to noxious stimuli were found.[10] Whether this may apply to other anaesthetics is unknown. The suppression of the movement response to noxious stimulation, therefore, might require other inhibitory effects additional to those on dorsal horn neurones, for example, a direct effect on ventral horn motor neurones, and supraspinal modulatory influences. The latter have been uncovered in the goat model when, with a low isoflurane concentration delivered to the spinal cord, dosal horn nociceptive responses increased with decreasing central isoflurane concentrations (Fig. 6).[9 62]

In conclusion, in most studies anaesthetics were shown to induce a decrease in the RF sizes and/or suppression of responses of nociceptive and non-nociceptive spinal cord neurones. For anaesthetic doses in the clinically relevant range this suppression of neuronal activity, however, is incomplete. The anaesthetic-induced suppression of pain-induced movements, therefore, may require suppression of activity at several sites, for example, in spinal dorsal and ventral horns and at supraspinal sites. Furthermore, response characteristics, for example, sustained discharge during stimulus presentation, are usually preserved (see Figs 3, 4

and 6). However, apart from RF sizes, detailed studies considering other properties of encoding stimulus information, such as velocity of movement, strength of pressure, duration, or vibration are largely missing. Results from studies using spinal cord transection and/or decerebration might have been confounded by effects of the gross surgical interventions and the removal of descending modulatory influences. Surprisingly, few *in vivo* studies so far have addressed in detail the question of 'how?' do anaesthetics affect spinal cord information processing.

Brain stem

In general, a distinction is made between the 'specific' sensory systems and the 'unspecific' sensory system, of which the brain stem reticular formation is an important component. It is, amongst other things, involved in the control of arousal reactions, the sleep–wake cycle, or vegetative/autonomic responses. The TRN is considered a diencephalic extension of the brain stem reticular formation (see below). This multimodal system receives its 'specific' somatosensory input from collaterals of the ascending tracts. Its major efferent connections are to the cortex via the thalamus, to the limbic system, the hypothalamus, and the spinal cord. It exerts descending modulatory effects (inhibition and excitation) on the activity of spinal neurones via bulbospinal pathways (e.g. from the PAG and rostral ventral medulla); for example, tonic inhibition from the brain stem can decrease responsiveness and RF size of spinal somatosensory neurones. The brain stem reticular formation, thus, may play a central role in mediation of the anaesthetic-induced suppression of CNS neuronal activity.

Numerous studies investigated the effects of anaesthetics on the discharge activity of brain stem reticular neurones after sensory stimulation, and most of them described an anaesthetic-induced decrease in firing rates. One such study assessed the effects of thiopental on discharges of nucleus reticularis gigantocellularis neurones in decerebrate cats.[63] The authors demonstrated a dose-dependent decrease of ongoing and evoked (electrical stimulation of Aδ-fibres) discharges which was comparable with the effects of halothane, nitrous oxide, morphine, and ketamine.[24 65 85] The local administration of ketamine by microiontophoresis, however, did not cause a change in the spontaneous firing rate of midbrain neurones.[1] Shimoji's group[99–102] described differential effects on midbrain reticular neurones, that is they found suppressed excitatory responses to sensory stimulation under most anaesthetics and potentiated inhibitory responses under barbiturates and deep inhalation anaesthesia.

The neurones in the pontomedullary raphe magnus and nucleus reticularis paragigantocellularis have been implicated to modulate spinal nociceptive transmission. Leung and colleagues[72] showed that isoflurane did not activate the putative inhibitory output neurones, and concluded that these neurones do not contribute to the obliteration of nocifensive movements by isoflurane. The effects of pentobarbital[79] and chloral hydrate[58] in the dorsal raphe nucleus were also studied in awake *vs* anaesthetized animal preparations. Heym and colleagues[58] found only a slight anaesthetic-induced decrease in spontaneous firing rate of serotonergic dorsal raphe nucleus neurones but a complete abolition of excitatory responses to auditory and visual stimuli.

The ventromedial medulla is another part of the descending control system involved in spinal nociceptive transmission. A comparison of the properties of ventromedial medullary neurones between the awake *vs* anaesthetized state revealed that responses to noxious stimulation were suppressed by methohexital and pentobarbital; in contrast, responses to innocuous stimulation were less affected.[86 87] Based on the assumption that anaesthetics may interact with descending spinal control mechanisms, it still has to be elucidated in detail how anaesthetics may enhance descending inhibition.[55]

As the ventral tegmental area (VTA) is thought to participate in the control of behavioural arousal and excitation of cortical structures, studies have assessed the effects of anaesthetics on the activity of components of this midbrain system. The VTA dopaminergic neurones were shown not to be affected by anaesthetics.[77 105] A recent study using freely behaving rats assessed the effects of halothane, ketamine, and chloral hydrate on the discharges of VTA GABAergic neurones.[70] It was shown that adequate anaesthesia (determined by the absence of nocifensive movements) caused a decrease of the discharge rate and an alteration of the discharge pattern (Fig. 7) suggesting that this part of the extrathalamic cortical activating system may be significantly affected by anaesthetics. However, all the studies cited above share one general feature in that it remains unclear whether the changes in brain stem neuronal firing are causative for the production of the anaesthetic state or whether they constitute epiphenomena.

Another interesting circuitry of the brain stem is the neuronal population involved in the generation and control of breathing, which is spontaneously active during wakefulness and anaesthesia. Zuperku's group[108] showed that the suppressive effects of a 1 MAC concentration increase of halothane on medullary expiratory neurones is mainly induced by a depression of glutamatergic neurotransmission and not by a potentiation of GABAergic inhibition. This was confirmed using a decerebrate dog model allowing for a drug-free baseline.[107 109] The mathematical model of analysis used in these studies has also been applied in experiments on thalamic neurones.[39]

Thalamus

A key location for modulation of the ascending sensory signals is the thalamus as it is the immediate input stage to the cerebral cortex. In early studies[93] no changes in RF characteristics of primate thalamic neurones were found

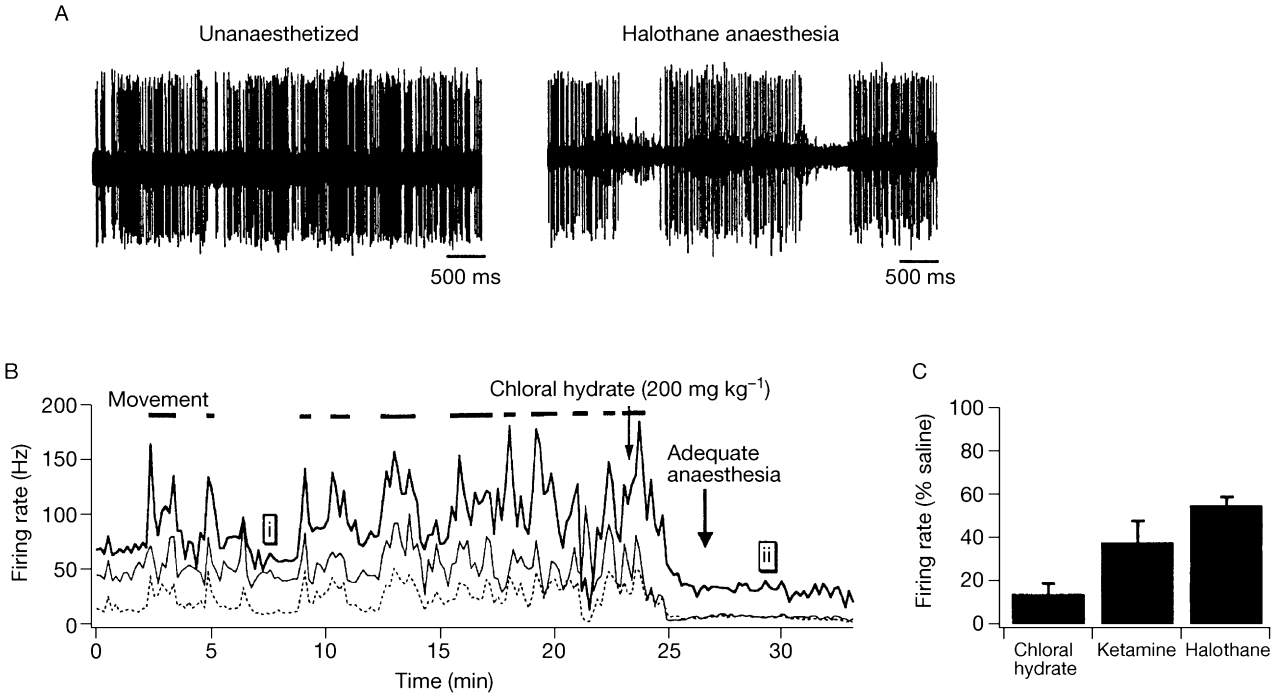

Fig 7 Comparison of the discharge activity of GABAergic neurones in the VTA in awake and halothane-anaesthetized rats. (A) In the awake condition, the discharges are regular whereas in the halothane-anaesthetized condition phasic firing with on/off periods and a lower discharge rate dominates. (B) Rate meter records depicting the simultaneous recordings from three VTA neurones in freely behaving rats and the effects of induction of anaesthesia by chloral hydrate (200 mg kg^{-1}). The anaesthetic strongly depresses the activity of two neurones and modestly affects the discharge rate of the remaining one. (C) Effects of three different anaesthetics on discharge rate of VTA neurones as compared with the awake state (100%; $*P<0.05$). The animals were adequately anaesthetized to the same clinical endpoint as determined by the absence of responses to tail pinch (from[70]).

with increasing anaesthetic depth, while later studies reported a decrease of response activity especially for nociceptive neurones in rats and cats under chloralose, pentobarbitoal, or urethane anaesthesia.[50 52 92] In contrast, increases of LTM responses and RF sizes were reported with increasing anaesthetic depth.[50] When compared with the awake state, the proportion of different response classes encountered in the rat thalamus changed: HT neurones were only found during pentobarbital anaesthesia,[78] while no difference in the neuronal classes sampled was found in the racoon under varying anaesthetic states,[103] and in monkeys under halothane and pentobarbital.[41]

Dougherty and co-workers[41] correlated EEG measurements with thalamic single neurone responsiveness. On a background pentobarbital anaesthetic, a low dose of halothane (0.25%) produced a facilitation of cutaneous responses and a decrease in rate and burst pattern of ongoing activity, with no change in EEG; 0.5–1% halothane produced no change in ongoing activity and the evoked responses returned to baseline, with a concomitant reduction in EEG power; 2–3% halothane induced a suppression of all variables. In contrast, methohexital given on a background halothane anaesthetic produced a reduction in EEG power at a low dose, but no change in responses or ongoing activity; only at high doses was a suppression of all variables found. Halothane decreased RF sizes and abolished nociceptive responses at concentrations when low-threshold responses were still present, while methohexital had no effect on RF sizes and preferentially affected low-threshold responses. Although the results point to different mechanisms of action for halothane and methohexital, the results are difficult to interpret or to translate to other models, as the individual effects of the two anaesthetics cannot be differentiated.

Many of the discrepancies observed for thalamic responsiveness and organization probably result from differences in the anaesthetics *per se* and/or the doses used in the different studies. Again, a comparison with a drug-free baseline might shed some light on the causes of some of the discrepancies. In an early study, Baker[14] showed that responses and the surprisingly large RFs of VB neurones in the cat were unchanged during different stages of wakefulness, but that the rate of ongoing activity was high and regular during wakefulness and bursting during sleep and pentobarbital anaesthesia. In contrast, Morrow and Casey[81 82] demonstrated that processing of mechanoreceptive and nociceptive somatosensory information in VB of the monkey was modulated during changes of arousal in the awake animal (see also above). All somatosensory submodalities (hair, skin, deep, LT, and WDR) were affected and a mean change of 40% in evoked activity was seen. Arousal-related changes were independent of changes in ongoing activity. Most neurones responded maximally

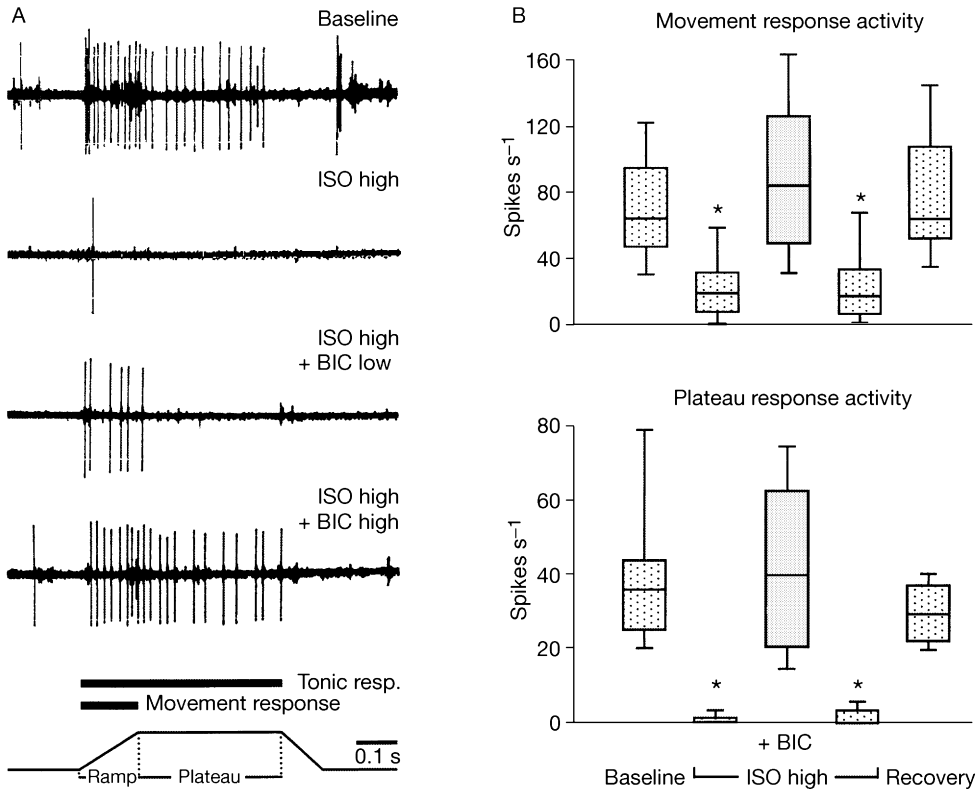

Fig 8 Local $GABA_A$ receptor antagonism reverses the isoflurane-induced inhibition of the tonic responses of thalamic neurones. (A) The tonic response of a VB neurone present under baseline anaesthesia (0.6% isoflurane) is converted to an ON spike under ISO high (1.0% isoflurane). During ejection of the $GABA_A$ receptor antagonist bicuculline (BIC) the response recovers dose-dependently with time: first the movement response appears, then the plateau response. Original spike records of single responses to trapezoidal movement of a whisker (lowest trace). (B) Suppression of response discharges of 23 VB neurones by high isoflurane concentrations (ISO high, 1.0–1.8%) and reversal by BIC. BIC significantly increased the response activity measured during the entire stimulus and during the ramp and plateau parts of the stimulus. Baseline: 0.6 or 0.8% isoflurane. Recovery: return to baseline isoflurane concentration. *P<0.001 *vs* baseline (modified from[116]).

during quiet waking, fewer during drowsiness, and fewest during waking movement state.

The whisker system of rats and cats has been used extensively as a model for studies of somatosensory information processing, because facial whiskers arranged around the snout drive all types of mechanoreceptors also present in the human skin. Selective effects of halothane/urethane anaesthesia on inputs from the spinal trigeminal nucleus interpolaris (Sp5i) to thalamic VB neurones as opposed to inputs from the principal trigeminal nucleus (Pr5) were studied by Friedberg and colleagues.[45] In rats, Sp5i mediates larger RFs (mean, five to eight whiskers), whereas Pr5 mediates single-whisker RFs; however, most studies on VB neurones in anaesthetized rats report single-whisker RFs. It was found that deeper levels of anaesthesia, as determined by dominant EEG/ECoG frequency, selectively gated the influence of Sp5i inputs on VB neurone responses. With lighter levels of anaesthesia, RF sizes and peak onset latency of responses increased, while response probability and magnitude decreased. The question remains, whether the anaesthetic affected presynaptic or postsynaptic sites in the thalamus, or caused reduction of RF size and change in response properties by suppression of neurones in the brain stem Sp5i nucleus. Nevertheless, this study demonstrates a differential effect of an anaesthetic onto processing of information about the stimulus characteristics represented in a sensory modality.

Our own studies with isoflurane in rats have shown dissociation between anaesthetic effects on the tactile and nociceptive systems. A feedback inhibition is exerted by GABAergic neurones of the TRN onto both VB and PO neurones (see Fig. 1). This provides a pathway for modulation and filtering of ascending sensory information that is a general feature of the thalamic stage within sensory systems. In higher mammals including humans, thalamic sensory nuclei also contain intrinsic GABAergic interneurones rendering the inhibitory network even more complex. The cerebral cortex thus receives information that is strongly filtered and modulated; for example, according to the stimulation situation of the sense organs, the degree of attention, or the sleep–wake situation—hence the thalamus may be a strategic target for anaesthetics? We have shown in this model that isoflurane changes the functional characteristics of thalamic somatosensory information transfer.[37] Tonic responses mediating information about the extent of deflection and movement velocity

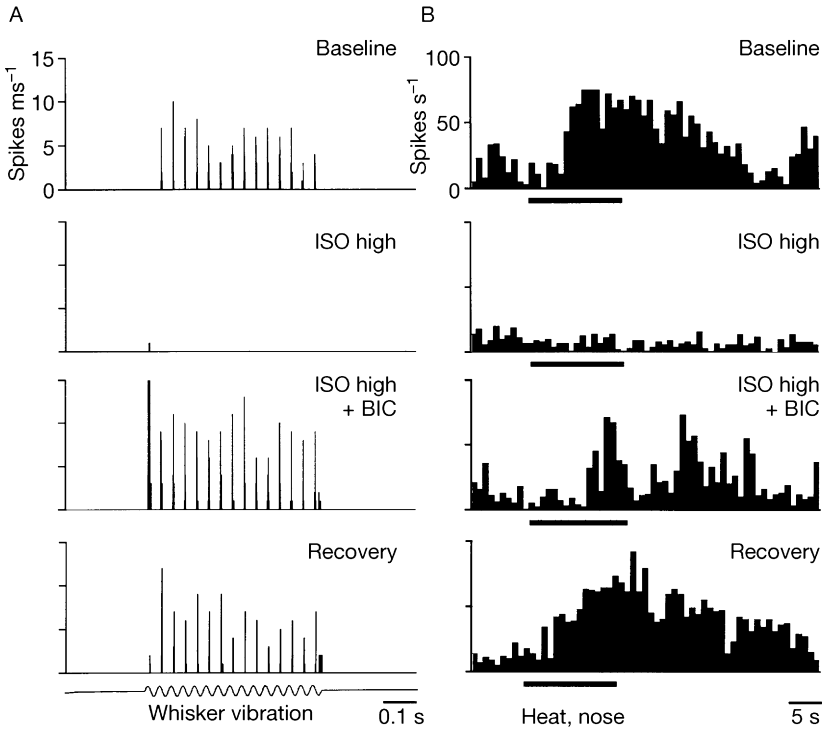

Fig 9 Local block of $GABA_A$ receptors fully antagonizes the suppressive effects of isoflurane on LTM and partly on HT thalamic neurones. (A) 1.8% isoflurane abolishes the phase-coupled vibratory responses of a LTM neurone present under baseline anaesthesia (1.0% isoflurane) and bicuculline (BIC) administration removes the response suppression. Recovery of the tactile response after return to baseline conditions. Note that the response pattern (tight phase-coupling to vibration) is restored under BIC. Spike histograms (bin width 1 ms) were calculated from the neuronal responses to 20 consecutive stimulus presentations. (B) 1.2% isoflurane abolishes the heat-evoked response of a thalamic HT neurone present under baseline anaesthesia (0.9% isoflurane) and BIC administration partly removes the response suppression. Recovery of the nociceptive response after return to the baseline condition. Spike histograms, bin width 1 s; the bar below each histogram represents the duration of the heat stimulus (B, modified from[117]).

of a whisker (Fig. 8), and sustained vibratory responses (Fig. 9A), were converted to phasic on-responses. Thus, information about stimulus characteristics was lost during anaesthesia with high concentrations of isoflurane. Using local microiontophoretic administration of GABA and its receptor antagonist to the neurones under study, it was found that the enhancement of thalamic $GABA_A$ergic inhibition appears to be the major target for suppression of LTM neuronal activity (Figs 8 and 9A[116]). Nociceptive responses, on the other hand, appeared to be suppressed to a great extent at subthalamic sites (Fig. 9B[117]). This is in line with results of a study on nociceptive neurones of the medial thalamus in the goat model (see above), where low concentrations of isoflurane administered to the torso circulation allowed nociceptive signal transmission to the thalamus but hindered thalamic responses at a higher concentration.[11] The arousal effect of noxious stimulation reflected in EEG power decrease was abolished in a similar way by increasing torso concentration from 0.3 to 1.0% or cranial concentration from 1.3 to 1.7% isoflurane.

Neurones within the somatotopically organized lateral striatum receive topographic projections from SI and MI cortices and respond to mechanical stimulation of the peripheral RF in awake rats.[121] The same neurones are dose-dependently suppressed and finally stop discharging in response to natural stimulation during anaesthesia (pentobarbital, ketamine, chloral hydrate, or urethane). The author suggested that glutamatergic inputs from SI cortex may still be intact under anaesthesia; however, the firing threshold of striatal neurones may be increased because of anaesthetic-induced changes of GABAergic or other membrane channel mechanisms.

Cortex

Most studies addressing cortical effects of anaesthetics have used recordings of potentials evoked by electrical or natural stimulation of the RF of neurones. As discussed earlier, these allow the anaesthetic effects to be localized, but conceal the neuronal mechanisms involved.

Somatosensory-evoked potentials (SEPs) in the rat proved to be least affected by fentanyl/fluanisone-midazolam anaesthesia when compared with ketamine-xylazine, medetomidine, and isoflurane.[54] A differential influence on SEPs and motor-evoked potentials (MEPs) was shown, for example, for enflurane in monkeys.[106] While SEPs elicited by median and posterior tibial nerve stimulation remained stable apart from amplitude reduction, MEPs, elicited by transcranial magnetic stimulation, were attenuated dose-dependently and were finally abolished by 0.25–1.0 MAC of

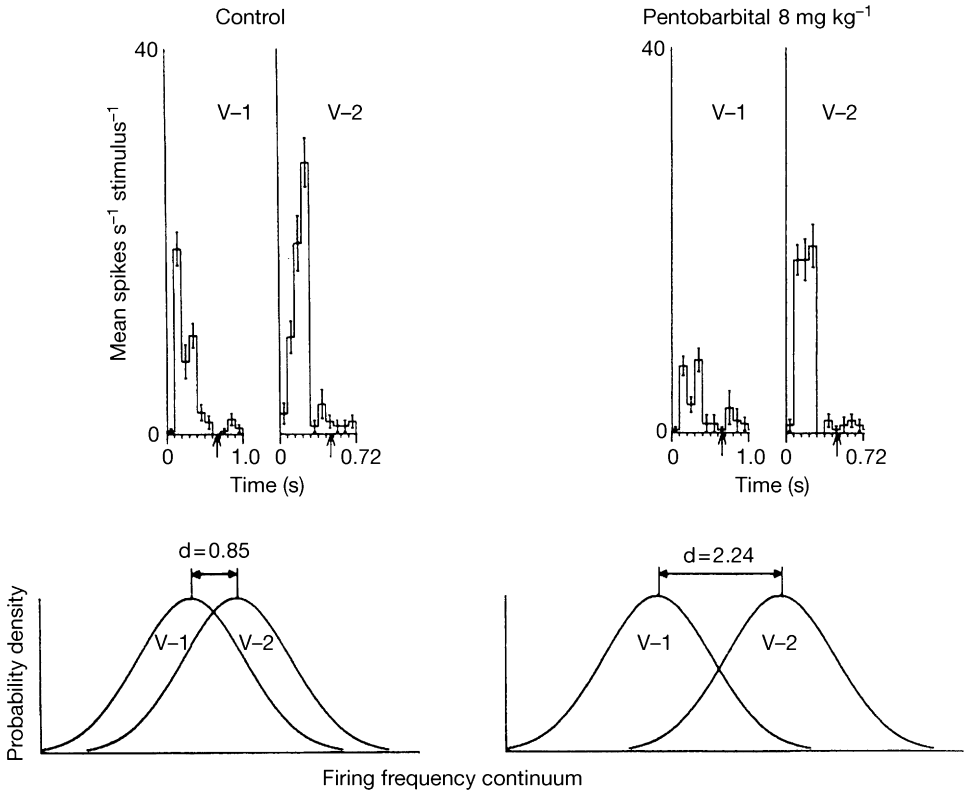

Fig 10 Pentobarbital-induced change in firing rate of a SI neurone in response to slow and fast movements of a brushing stimulus. Responses are compared between the physiologically intact drug-free awake state (control) and the anaesthetized state in a monkey. The stimulus was moved at 132 (V-1) and 182 (V-2) mm s^{-1} across the RF on the palmar surface of the hand (arrow: stimulus end). Stimulus velocity is encoded in the peak discharge rate during control and pentobarbital (upper histograms). Although the overall level of activity is reduced under pentobarbital, the difference between the mean discharge rates (expressed in standard deviation units, d) elicited by the two stimulus velocities is enhanced, as presented schematically in the lower plots (from[23]).

enflurane. MEPs were subjected to progressive elevation of threshold and reduction of effective scalp zone. These effects were attributed to central mechanisms, because MEPs elicited by spinal cord stimulation were unaffected. Etomidate, in contrast, even in concentrations inducing burst-suppression of the EEG, had no effect on SEPs recorded spinally and centrally and on early peaks of spinally recorded MEPs.[47]

A differential influence of pentobarbital on Aβ-fibre-mediated mechanical-evoked potentials and Aδ- and C-fibre-mediated mechanical or laser-evoked potentials (LEPs) was shown in rats.[98] While the former appeared to be facilitated, the latter were inhibited. The components returned with different time courses, LEPs being last, when the rat returned to wakefulness and began to exhibit coordinated movements.

The middle latency auditory-evoked potential (MLAEP) may be used as a measure of arousal and hence awareness during anaesthesia[19] and to demonstrate the responsiveness of the auditory system. Amplitudes of the MLAEP components were decreased and latencies increased under ketamine, xylazine, and propofol anaesthesia in guinea pigs and rats, but the response threshold to electrical or acoustic stimulation remained unchanged.[30 31 51] The recovery of the wave after propofol anaesthesia correlated with behavioural measures of the regaining of consciousness, but not with nocifensive movements.

The other approach, recording activity from single cortical neurones allows the study of the effects of anaesthesia on response properties reflecting details in the processing of sensory information. In single neurones of the primary somatosensory cortex (SI) of awake monkeys, velocity of brush movement across a cutaneous RF was encoded by different discharge rates but discrimination between different velocities was much poorer in most SI neurones than when a similar task was performed by humans.[23] Non-anaesthetic doses of pentobarbital caused a reduction in the overall discharge rate but enhanced the difference in response rate to two different stimulus velocities by greater suppression of the low velocity response (Fig. 10). It was speculated that under low doses of barbiturates, detection of stimuli might be impaired, but discrimination enhanced. In rats, an increase from light to deep anaesthesia by the steroid anaesthetic agent althesin induced a reduction of RF sizes with respect to discharge rates and responsiveness to stimulus repetition rates

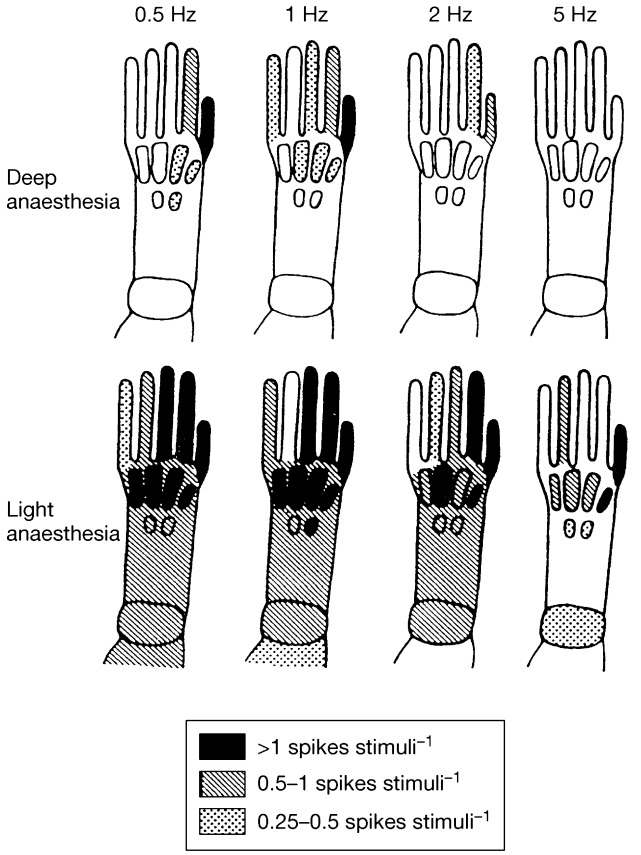

Fig 11 Changes in RF sizes, response magnitude, and responsiveness to stimulus repetition rates (0.5–5 Hz) in a neurone of the primary somatomotor cortex of the monkey under two levels of anaesthesia (althesin). Punctate stimuli at 1.5 times threshold of the RF centre under light anaesthesia were applied by a servocontrolled electromechanical probe to a standard set of discrete sites on the hind foot volar surface. The size of the RF decreases with increase of anaesthetic depth and stimulus repetition rate. The sensitivity of different parts of the RF changes with the stimulus repetition rate (from[13]).

(Fig. 11).[13] Whether this was caused by the effects of the anaesthetic in the cortex or reflected changes already present in the spinal cord remains to be determined.

Using chronically implanted microelectrodes, the effects of ketamine were studied simultaneously in up to six neurones of the SI cortex for several days in rats behaving in a treadmill movement paradigm.[90] Ketamine was shown to exert two opposing effects: (1) a complete inhibition of all somatosensory responsiveness, including suppression of activity related to active limb movement and (2) a tonic excitation of a subgroup (one-third) of cortical neurones persisting in a dose-dependent manner. The complete suppression of somatosensory responses by ketamine was in contrast to the selective suppression of long-latency but not short-latency sensory responses by halothane and barbiturates.[21] An earlier study,[64] however, interpreted ketamine effects to result in a concurrent increase of neocortical and hippocampal activity, as seen in markedly enhanced evoked potential and single neurone activity in the somatosensory and visual cortices.

Single neurone responses to sound were compared in the primary auditory cortex of cats anaesthetized first with isoflurane and then with pentobarbital.[22] Compared with pentobarbital, isoflurane had a profound impact on response sensitivity (higher thresholds, longer latencies) and temporal response properties of auditory cortical neurones. Periodic click trains, for example, were limited to an initial phase response to the first click element under isoflurane, while under pentobarbital responses were entrained to clicks of varying rates.

Direct comparison of effects of anaesthetics at different stages of ascending pathways

A differential suppression of 'non-specific' (MRF, medial thalamus) rather than 'specific' somatosensory, visual, and auditory regions was noted for barbiturates, ether, and halothane as demonstrated in EEG and evoked potential studies (for review[97]). Sparks and co-workers[104] using tooth pulp stimulation, recorded evoked potentials in the midbrain reticular formation (MRF), thalamus, and cortex in monkeys. Ketamine markedly reduced or obliterated evoked potentials in MRF and medial thalamus, while little effect was seen in the specific sensory thalamic nucleus, which is the VB. Anaesthetic doses of ketamine, thus, were shown to block afferent signals mediating affective-emotional components of pain perception, but to spare the sensory-discriminative component. The effects of pentobarbital and ketamine-xylazine anaesthesia on somatosensory cortical, brain stem auditory, and peripheral sensory-motor-evoked potentials were studied in the rat.[48] The results suggested that ketamine-xylazine affects synaptic transmission at the cortex and its communication with the thalamus, while pentobarbital seems to have a more generalized depressive effect in the CNS. Neither anaesthetic affected peripheral sensory or motor conduction, or the early components of the brain stem auditory response.

In a study on the effects of ketamine and/or pentobarbital on thalamic and cortical auditory neurones, Zurita and colleagues[128] found that the two anaesthetics had different and sometimes opposite effects suggesting different sites of action. Ketamine increased the acoustically evoked peak response rate in the majority of thalamic neurones, whereas it was decreased in the majority of cortical neurones (Fig. 12). In both regions, the ongoing activity generally decreased; however, with a differential effect on burst pattern by pentobarbital and ketamine. In general, not only the discharge rates changed but also the pattern of discharges in response to stimulation. This, for example, pertained to an increase in tonal selectivity, and hence affected the functional properties of the neurones reflecting their involvement in the processing of sensory information.

The most extensive studies on the effects of anaesthetics at several hierarchical sites of the CNS have been done by

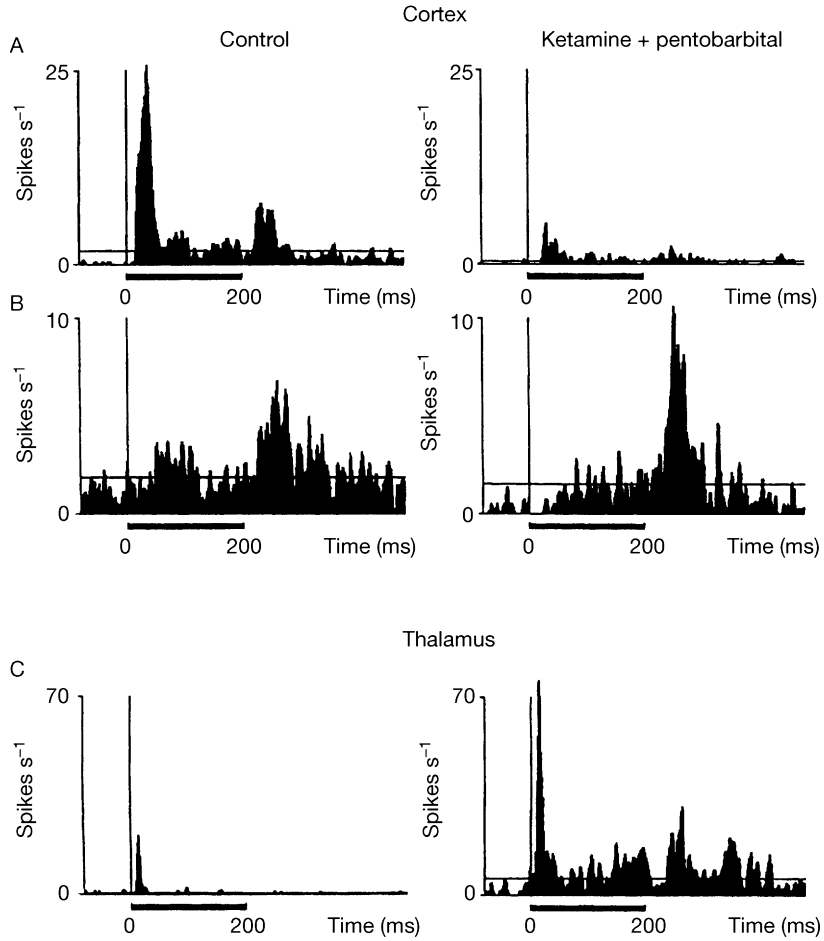

Fig 12 Differential effects of a mixture of ketamine and pentobarbital on responses of two cortical (A and B) and a thalamic neurone (C) to acoustic stimulation (white noise bursts of 200 ms duration, horizontal bars) in nitrous oxide anaesthetized cats. The additional anaesthetics induce a decrease of firing rates of the transient onset and offset responses in one cortical neurone (A), but an increase of the offset response in another cortical neurone (B), while an overall increase of the thalamic response is seen in (C). Horizontal lines correspond to the upper 99% confidence level (from[128]).

Angel (for reviews[3 5 6]). Most anaesthetics including volatile anaesthetics, barbiturates, nitrous oxide, and ketamine were shown to cause their effects by increased inhibition and decreased excitation of the thalamo-cortico-reticular circuitry. Some differential effects were seen with etomidate and benzodiazepines, and for propofol, the primary somatosensory cortex was suggested to be the major site of action.[4] These results were derived from recordings of responses of dorsal column, thalamic, and cortical neurones to electrical stimulation applied to the wrist of the rat. Responses of neurones in dorsal column nuclei in urethane-anaesthetized rats were found to be barely affected by isoflurane at concentrations up to 3%.[3 5 6] Synaptic efficiency may even be potentiated in the dorsal column nuclei of the decerebrate cat by pentobarbital and halothane and previous reports emphasize the remarkably high safety factor of signal transmission at this stage in the ascending pathway.[80] Similarly, the synaptic transmission to the thalamic VB neurones, that is at the next stage, is also characterized by a high safety factor under various conditions of anaesthesia.[2 115] In VB neurones, approximately 3% isoflurane administered on background urethane anaesthesia induced an increase of response latency for only about 1–2 ms and a modest decrease in response probability.[3 5 6]

In our experiments[37 38] we used acute single neurone recordings in the ascending tactile pathway (Pr5, VB, SI; see Fig. 1) of the rat. These studies go beyond Angel's pioneering work by using adequate stimuli for activation of the different types of mechanoreceptors and thereby enabling assessment of central neuronal response characteristics underlying tactile information processing. For the typical Pr5 neurone shown in Figure 13A, an increase in isoflurane concentration from 0.9 to 1.9% caused only a modest decrease in the response rate but no change of the response pattern (with its one-to-one discharges occurring phase-coupled to the cycles of the whisker vibration). In VB neurones, in contrast, the response pattern was altered fundamentally by the high isoflurane concentration, which is that all stimulus-encoding features of the response were absent (Fig. 13B); a similar degree of response suppression

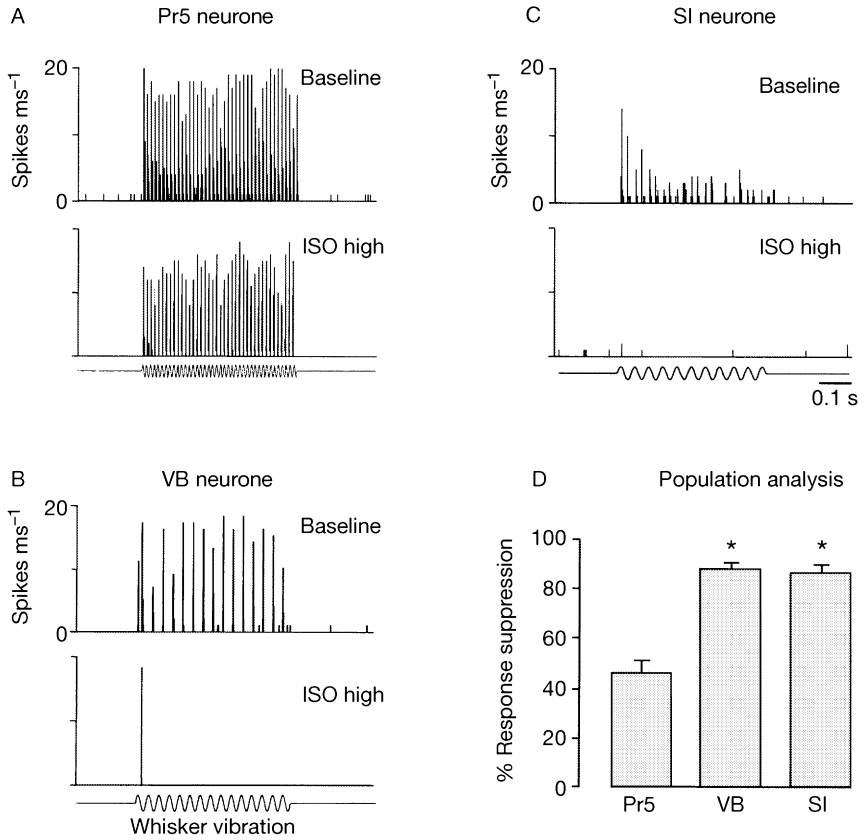

Fig 13 Differential effects of high isoflurane concentration (~1.9%) on processing of tactile information in successive stages of the ascending pathway. (A) The response characteristics of a trigeminothalamic neurone (principal trigeminal nucleus, Pr5) seen under baseline anaesthesia (~0.9% isoflurane) are preserved qualitatively under ISO high. In contrast, the response characteristics are changed fundamentally in a thalamo-cortical (VB complex) (B) and a cortical neurone (primary somatosensory cortex, SI) (C). Spike histograms (bin width 1 ms) in (A–C) were calculated from the neuronal responses to 20 stimulus repetitions. (D) Relative effects of high isoflurane concentration on response activities of all three classes of neurones. The high isoflurane concentration causes a profound suppression of thalamo-cortical signal transmission, whereas the subthalamic pathway is only moderately affected. *P<0.001 *vs* Pr5 (modified from[38]).

was seen at the cortical level (Fig. 13C). The population also demonstrated the high susceptibility of the thalamo-cortical system to the depressive effects of isoflurane as compared with the subthalamic site (Fig. 13D). As the response activity encodes intensity, velocity, and duration of a mechanical stimulus affecting the body surface, this information is suppressed under higher isoflurane concentrations because of the predominant thalamic block of sensory signalling. However, again, these studies compared changes in neuronal firing induced by an increase in anaesthetic dose and did not study the effects of the anaesthetic *per se*.

A general feature noted in many studies was that anaesthetic-induced effects on ongoing and stimulus-evoked activity were unrelated. This observation applies to all stages of the ascending sensory pathways (see above) and may indicate that anaesthetic effects on the basal level of excitation of the neurones and on their modes of processing of sensory information may employ different mechanisms. Also, differential susceptibility to anaesthetic effects was noted for different sensory modalities (e.g. touch *vs* pain) and characteristics (e.g. tonic *vs* phasic responses, certain RF characteristics). The suppressive effects on stimulus-evoked neuronal responses in most cases, particularly in LTM neurones, were incomplete at the spinal cord level, even under high doses of anaesthetics, and responses were only abolished at the thalamic and cortical level, indicating a gradual reduction of information flow in the ascending pathways.

Conclusion

In vitro studies have provided insights into a great number of mechanisms of anaesthesia on the subcellular, cellular, and network level. The relative impact of effects demonstrated in those artificial preparations, however, has to be validated in fully intact *in vivo* preparations to elucidate their contribution to the production of the anaesthetic state. Many of the animal studies that addressed that question, however, have been hampered by the shortcomings inherent to animal models. The ideal animal model still does not exist and, therefore, the experimental designs, preparations

and procedures implemented to date require further refinements to overcome their present limitations. The selection of appropriate recording sites is critical, CNS areas producing consciousness, cognitive functioning, perception and memory, however, have not been unequivocally identified yet, rendering the assessment of the 'where?' of anaesthetic action difficult. As long as it is not understood how neuronal activity translates into higher brain functions, measuring neuronal discharges will hardly enable the mechanisms underlying the anaesthetic-induced suppression of these functions to be pinpointed. Nevertheless, some *in vivo* animal studies have successfully tested the hypotheses put forward from *in vitro* findings and, thus added valid pieces to the jigsaw of 'where and how do anaesthetics cause anaesthesia?'.

References

1 Aida S, Fujiwara N, Shimoji K. Differential regional effects of ketamine on spontaneous and glutamate-induced activities of single CNS neurones in rats. *Br J Anaesth* 1994; **73**: 388–94

2 Alloway KD, Wallace MB, Johnson MJ. Cross-correlation analysis of cuneothalamic interactions in the rat somatosensory system: influence of receptive field topography and comparisons with thalamocortical interactions. *J Neurophysiol* 1994; **72**: 1949–72

3 Angel A. The G. L. Brown lecture. Adventures in anaesthesia. *Exp Physiol* 1991; **76**: 1–38

4 Angel A, LeBeau F. A comparison of the effects of propofol with other anaesthetic agents on the centripetal transmission of sensory information. *Gen Pharmacol* 1992; **23**: 945–63

5 Angel A. Central neuronal pathways and the process of anaesthesia. *Br J Anaesth* 1993; **71**: 148–63

6 Angel A. How do anaesthetics work? *Curr Anaesth Cri Care Pharmacol* 1993; **4**: 37–45

7 Antognini JF, Schwartz K. Exaggerated anesthetic requirements in the preferentially anesthetized brain. *Anesthesiology* 1993; **79**: 1244–9

8 Antognini JF, Kien ND. Potency (minimum alveolar anesthetic concentration) of isoflurane is independent of peripheral anesthetic effects. *Anesth Analg* 1995; **81**: 69–72

9 Antognini JF, Carstens E, Tabo E, Buzin V. Effect of differential delivery of isoflurane to head and torso on lumbar dorsal horn activity. *Anesthesiology* 1998; **88**: 1055–61

10 Antognini JF, Carstens E. Increasing isoflurane from 0.9 to 1.1 minimum alveolar concentration minimally affects dorsal horn cell responses to noxious stimulation. *Anesthesiology* 1999; **90**: 208–14

11 Antognini JF, Carstens E, Sudo M, Sudo S. Isoflurane depresses electroencephalographic and medial thalamic responses to noxious stimulation via an indirect spinal action. *Anesth Analg* 2000; **91**: 1282–8

12 Antognini JF, Wang XW, Piercy M, Carstens E. Propofol directly depresses lumbar dorsal horn neuronal responses to noxious stimulation in goats. *Can J Anaesth* 2000; **47**: 273–9

13 Armstrong-James M, George MJ. Influence of anesthesia on spontaneous activity and receptive field size of single units in rat Sm1 neocortex. *Exp Neurol* 1988; **99**: 369–87

14 Baker MA. Spontaneous and evoked activity of neurones in the somatosensory thalamus of the waking cat. *J Physiol* 1971; **217**: 359–79

15 Bosnjak ZJ, Seagard JL, Wu A, Kampine JP. The effects of halothane on sympathetic ganglionic transmission. *Anesthesiology* 1982; **57**: 473–9

16 Bromberg MB, Fetz EE. Responses of single units in cervical spinal cord of alert monkeys. *Exp Neurol* 1977; **55**: 469–82

17 Cairns BE, McErlane SA, Fragoso MC, Soja PJ. Tooth pulp- and facial hair mechanorecptor-evoked responses of trigeminal sensory neurons are attenuated during ketamine anesthesia. *Anesthesiology* 1999; **91**: 1025–35

18 Campbell JN, Raja SN, Meyer RA. Halothane sensitizes cutaneous nociceptors in monkeys. *J Neurophysiol* 1984; **52**: 762–70

19 Cardenas VA, McCallin K, Hopkins R, Fein G. A comparison of the repetitive click and conditioning-testing P50 paradigms. *Electroencephalogr Clin Neurophysiol* 1997; **104**: 157–64

20 Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature* 1997; **389**: 816–24

21 Chapin JK, Waterhouse BD, Woodward DJ. Differences in cutaneous sensory response properties of single somatosensory cortical neurons in awake and halothane anesthetized rats. *Brain Res Bull* 1981; **6**: 63–70

22 Cheung SW, Nagarajan SS, Bedenbaugh PH, Schreiner CE, Wang X, Wong A. Auditory cortical neuron response differences under isoflurane versus pentobarbital anesthesia. *Hear Res* 2001; **156**: 115–27

23 Collins JG, Roppolo JR. A comparison of human tactile stimulus velocity discrimination with the ability of S-I cortical neurons in awake rhesus monkeys to signal the same velocity differences before and after non-anesthetic doses of pentobarbital. *Brain Res* 1980; **198**: 307–21

24 Collins JG, Kawahara M, Homma E, Kitahata LM. Alpha-chloralose suppression of neuronal activity. *Life Sci* 1983; **32**: 2995–9

25 Collins JG. A technique for chronic extracellular recording of neuronal activity in the dorsal horn of the lumbar spinal cord in drug-free, physiologically intact, cats. *J Neurosci Methods* 1985; **12**: 277–87

26 Collins JG, Ren K. WDR response profiles of spinal dorsal horn neurons may be unmasked by barbiturate anesthesia. *Pain* 1987; **28**: 369–78

27 Collins JG, Ren K, Saito Y, Iwasaki H, Tang J. Plasticity of some spinal dorsal horn neurons as revealed by pentobarbital-induced disinhibition. *Brain Res* 1990; **525**: 189–97

28 Collins JG, Kendig JJ, Mason P. Anesthetic actions within the spinal cord: contributions to the state of general anesthesia. *Trends Neurosci* 1995; **18**: 549–53

29 Conseiller C, Benoist JM, Hamann KF, Maillard MC, Besson JM. Effects of ketamine (CI 581) on cell responses to cutaneous stimulations in laminae IV and V in the cat's dorsal horn. *Eur J Pharmacol* 1972; **18**: 346–52

30 Crowther J, Cannon SC, Miller JM, Jyung RW, Kileny P. Anesthesia effects on the electrically evoked middle latency response in guinea pigs. *Otolaryngol Head Neck Surg* 1989; **101**: 51–5

31 Crowther JA, Miller JM, Kileny P. Effects of anesthesia on acoustically evoked middle latency response in guinea pigs. *Hear Res* 1990; **43**: 115–20

32 De Jong RH, Nace RA. Nerve impulse conduction and cutaneous receptor responses during general anesthesia. *Anesthesiology* 1967; **28**: 851–5

33 De Jong RH, Wagman IH. Block of afferent impulses in the dorsal horn of monkey. A possible mechanism of anesthesia. *Exp Neurol* 1968; **20**: 352–8

34 De Jong RH, Robles R, Corbin RW, Nace RA. Effect of inhalation

anesthetics on monosynaptic and polysynaptic transmission in the spinal cord. *J Pharmacol Exp Ther* 1968; **162**: 326–30

35 De Jong RH, Robles R, Morikawa KI. Actions of halothane and nitrous oxide on dorsal horn neurons ('The Spinal Gate'). *Anesthesiology* 1969; **31**: 205–12

36 De Jong RH, Robles R, Heavner JE. Suppression of impulse transmission in the cat's dorsal horn by inhalation anesthetics. *Anesthesiology* 1970; **32**: 440–5

37 Detsch O, Vahle-Hinz C, Kochs E, Siemers M, Bromm B. Isoflurane induces dose-dependent changes of thalamic somatosensory information transfer. *Brain Res* 1999; **829**: 77–89

38 Detsch O, Kochs E, Siemers M, Bromm B, Vahle-Hinz C. Suppression of tactile information transfer by isoflurane within the CNS. In: Urban BW, Barann M, eds. *Molecular and Basic Mechanisms of Anesthesia*. Berlin: Pabst Scientific Publishers, 2002; in press

39 Detsch O, Kochs E, Siemers M, Bromm B, Vahle-Hinz C. Differential effects of isoflurane on excitatory and inhibitory synaptic inputs to thalamic neurones *in vivo*. *Br J Anaesth* 2002; **89**: in press

40 Dodd F, Capranica RR. A comparison of anesthetic agents and their effects on the response properties of the peripheral auditory system. *Hear Res* 1992; **62**: 173–80

41 Dougherty PM, Li YJ, Lenz FA, Rowland L, Mittman S. Correlation of effects of general anesthetics on somatosensory neurons in the primate thalamus and cortical EEG power. *J Neurophysiol* 1997; **77**: 1375–92

42 Fanselow EE, Nicolelis MA. Behavioral modulation of tactile responses in the rat somatosensory system. *J Neurosci* 1999; **19**: 7603–16

43 Fields HL, Basbaum AI. Brainstem control of spinal pain-transmission neurons. *Annu Rev Physiol* 1978; **40**: 217–48

44 Franks NP, Lieb WR. Which molecular targets are most relevant to general anaesthesia? *Toxicol Lett* 1998; **100/101**: 1–8

45 Friedberg MH, Lee SM, Ebner FF. Modulation of receptive field properties of thalamic somatosensory neurons by the depth of anesthesia. *J Neurophysiol* 1999; **81**: 2243–52

46 Galindo A. Effects of procaine, pentobarbital and halothane on synaptic transmission in the central nervous system. *J Pharmacol Exp Ther* 1969; **169**: 185–95

47 Ghaly RF, Lee JJ, Ham JH, Stone JL, George S, Raccforte P. Etomidate dose-response on somatosensory and transcranial magnetic induced spinal motor evoked potentials in primates. *Neurol Res* 1999; **21**: 714–20

48 Goss-Sampson MA, Kriss A. Effects of pentobarbital and ketamine-xylazine anaesthesia on somatosensory, brainstem auditory and peripheral sensory-motor responses in the rat. *Lab Anim* 1991; **25**: 360–6

49 Gruneis F, Nakao M, Yamamoto M. Counting statistics of 1/f fluctuations in neuronal spike trains. *Biol Cybern* 1990; **62**: 407–13

50 Guilbaud G, Peschanski M, Gautron M. Functional changes in ventrobasal thalamic neurones responsive to noxious and non-noxious cutaneous stimuli after chloralose treatment: new evidence for the presence of pre-existing 'silent connections' in the adult nervous system? *Pain* 1981; **11**: 9–19

51 Haberham ZL, van den Brom WE, Venker-van Haagen AJ, de Groot HN, Baumans V, Hellebrekers LJ. The rat vertex-middle latency auditory-evoked potential as indicator of anaesthetic depth: a comparison with evoked-reflex testing. *Brain Res* 2000; **873**: 287–90

52 Harris FA. Functional subsets of neurons in somatosensory thalamus of the cat. *Exp Neurol* 1978; **58**: 149–70

53 Hartell NA, Headley PM. Preparative surgery enhances the direct spinal actions of three injectable anaesthetics in the anaesthetized rat. *Pain* 1991; **46**: 75–80

54 Hayton SM, Kriss A, Muller DP. Comparison of the effects of four anaesthetic agents on somatosensory evoked potentials in the rat. *Lab Anim* 1999; **33**: 243–51

55 Heinricher MM, Morgan MM, Fields HL. Direct and indirect actions of morphine on medullary neurons that modulate nociception. *Neuroscience* 1992; **48**: 533–43

56 Herrero JF, Headley PM. Cutaneous responsiveness of lumbar spinal neurons in awake and halothane-anesthetized sheep. *J Neurophysiol* 1995; **74**: 1549–62

57 Herrero JF, Headley PM. Sensitization of spinal neurons by non-noxious stimuli in the awake but not anesthetized state. *Anesthesiology* 1995; **82**: 267–75

58 Heym J, Steinfels GF, Jacobs BL. Chloral hydrate anesthesia alters the responsiveness of central serotonergic neurons in the cat. *Brain Res* 1984; **291**: 63–72

59 Hicks TP. The history and development of microiontophoresis in experimental neurobiology. *Prog Neurobiol* 1984; **22**: 185–240

60 Homma E, Collins JG, Kitahata LM, Matsumoto M, Kawahara M. Suppression of noxiously evoked WDR dorsal horn neuronal activity by spinally administered morphine. *Anesthesiology* 1983; **58**: 232–6

61 Hori Y, Lee KH, Chung JM, Endo K, Willis WD. The effects of small doses of barbiturate on the activity of primate nociceptive tract cells. *Brain Res* 1984; **307**: 9–15

62 Jinks S, Antognini JF, Carstens E, Buzin V, Simons C. Isoflurane can indirectly depress lumbar dorsal horn activity in the goat via action within the brain. *Br J Anaesth* 1999; **82**: 244–9

63 Kawahara M, Kitahata LM, Collins JG, Homma E. Thiopental suppression of neurons of the nucleus reticularis gigantocellularis of the cat. *Anesth Analg* 1982; **61**: 763–6

64 Kayama Y, Iwama K. The EEG, evoked potentials, and single-unit activity during ketamine anesthesia in cats. *Anesthesiology* 1972; **36**: 316–28

65 Kikuchi H, Kitahata LM, Collins JG, Kawahara M, Nio K. Halothane-induced changes in neuronal activity of cells of the nucleus reticularis gigantocellularis of the cat. *Anesth Analg* 1980; **59**: 897–901

66 Kishikawa K, Uchida H, Yamamori Y, Collins JG. Low-threshold neuronal activity of spinal dorsal horn neurons increases during REM sleep in cats: comparison with effects of anesthesia. *J Neurophysiol* 1995; **74**: 763–9

67 Kitahata LM, Kosaka Y, Taub A, Bonikos K, Hoffert M. Lamina-specific suppression of dorsal-horn unit activity by morphine sulfate. *Anesthesiology* 1974; **41**: 39–48

68 Kitahata LM, Ghazi-Saidi K, Yamashita M, Kosaka Y, Bonikos C, Taub A. The depressant effect of halothane and sodium thiopental on the spontaneous and evoked activity of dorsal horn cells: lamina specificity, time course and dose dependence. *J Pharmacol Exp Ther* 1975; **195**: 515–21

69 Larrabee MG, Pasternak JM. Selective action of anesthetics on synapses and axons in mammalian sympathetic ganglia. *J Neurophysiol* 1952; **15**: 91–114

70 Lee RS, Steffensen SC, Henriksen SJ. Discharge profiles of ventral tegmental area GABA neurons during movement, anesthesia, and the sleep–wake cycle. *J Neurosci* 2001; **21**: 1757–66

71 Lenz FA, Dostrovsky JO, Kwan HC, Tasker RR, Yamashiro K, Murphy JT. Methods for microstimulation and recording of single neurons and evoked potentials in the human central nervous system. *J Neurosurg* 1988; **68**: 630–4

72 Leung CG, Mason P. Effects of isoflurane concentration on the activity of pontomedullary raphe and medial reticular neurons in the rat. *Brain Res* 1995; **699**: 71–82

73 Lipski J, Bellingham MC, West MJ, Pilowsky P. Limitations of the technique of pressure microinjection of excitatory amino acids for evoking responses from localized regions of the CNS. *J Neurosci Methods* 1988; **26**: 169–79

74 MacIver MB, Tanelian DL. Volatile anesthetics excite mammalian nociceptor afferents recorded *in vitro*. *Anesthesiology* 1990; **72**: 1022–30

75 Marshall KW, Tatton WG, Bruce IC. A technique for recording of single neurons in the spinal cord of awake cat. *J Neurosci Methods* 1984; **10**: 249–57

76 Menon DK. Mapping the anatomy of unconsciousness—imaging anaesthetic action in the brain. *Br J Anaesth* 2001; **86**: 607–10

77 Miller JD, Farber J, Gatz P, Roffwarg H, German DC. Activity of mesencephalic dopamine and non-dopamine neurons across stages of sleep and walking in the rat. *Brain Res* 1983; **273**: 133–41

78 Montagne-Clavel J, Oliveras JL. Does barbiturate anesthesia modify the neuronal properties of the somatosensory thalamus? A single-unit study related to nociception in the awake-pentobarbital-treated rat. *Neurosci Lett* 1995; **196**: 69–72

79 Montagne-Clavel J, Oliveras JL, Martin G. Single-unit recordings at dorsal raphe nucleus in the awake-anesthetized rat: spontaneous activity and responses to cutaneous innocuous and noxious stimulations. *Pain* 1995; **60**: 303–10

80 Morris ME. Facilitation of synaptic transmission by general anaesthetics. *J Physiol* 1978; **284**: 307–25

81 Morrow TJ, Casey KL. Modulation of the spontaneous and evoked discharges of ventral posterior thalamic neurons during shifts in arousal. *Brain Res Bull* 1988; **21**: 433–8

82 Morrow TJ, Casey KL. State-related modulation of thalamic somatosensory responses in the awake monkey. *J Neurophysiol* 1992; **67**: 305–17

83 Nadeson R, Goodchild CS. Antinociceptive properties of propofol: involvement of spinal cord gamma-aminobutyric acid(A) receptors. *J Pharmacol Exp Ther* 1997; **282**: 1181–6

84 Namiki A, Collins JG, Kitahata LM, Kikuchi H, Homma E, Thalhammer JG. Effects of halothane on spinal neuronal responses to graded noxious heat stimulation in the cat. *Anesthesiology* 1980; **53**: 475–80

85 Ohtani M, Kikuchi H, Kitahata LM, *et al*. Effects of ketamine on nociceptive cells in the medial medullary reticular formation of the cat. *Anesthesiology* 1979; **51**: 414–7

86 Oliveras JL, Martin G, Montagne-Clavel J. Drastic changes of ventromedial medulla neuronal properties induced by barbiturate anesthesia. II. Modifications of the single-unit activity produced by Brevital, a short-acting barbiturate in the awake, freely moving rat. *Brain Res* 1991; **563**: 251–60

87 Oliveras JL, Montagne-Clavel J, Martin G. Drastic changes of ventromedial medulla neuronal properties induced by barbiturate anesthesia. I. Comparison of the single-unit types in the same awake and pentobarbital-treated rats. *Brain Res* 1991; **563**: 241–50

88 Olsen RW. The molecular mechanism of action of general anesthetics: structural aspects of interactions with GABA(A) receptors. *Toxicol Lett* 1998; **100/101**: 193–201

89 Ota K, Yanagidani T, Kishikawa K, Yamamori Y, Collins JG. Cutaneous responsiveness of lumbar spinal dorsal horn neurons is reduced by general anesthesia, an effect dependent in part on GABAA mechanisms. *J Neurophysiol* 1998; **80**: 1383–90

90 Patel IM, Chapin JK. Ketamine effects on somatosensory cortical single neurons and on behavior in rats. *Anesth Analg* 1990; **70**: 635–44

91 Perkel DH, Gerstein GL, Moore GP. Neuronal spike trains and stochastic point processes. I. The single spike train. *Biophys J* 1967; **7**: 391–418

92 Perl ER, Whitlock DG. Somatic stimuli exciting spinothalamic projections to thalamic neurons in cat and monkey. *Exp Neurol* 1971; **3**: 256–96

93 Poggio GF, Mountcastle VB. The functional properties of ventrobasal thalamic neurons studied in unanesthetized monkeys. *J Neurophysiol* 1963; **26**: 775–806

94 Puil E, Gimbarzevsky B. Modifications in membrane properties of trigeminal sensory neurons during general anesthesia. *J Neurophysiol* 1987; **58**: 87–104

95 Richards CD. Actions of general anaesthetics on synaptic transmission in the CNS. *Br J Anaesth* 1983; **55**: 201–7

96 Richards CD. The synaptic basis of general anaesthesia. *Eur J Anaesthesiol* 1995; **12**: 5–19

97 Rosner BS, Clark DL. Neurophysiologic effects of general anesthetics. II. Sequential regional actions in the brain. *Anesthesiology* 1973; **39**: 59–81

98 Shaw FZ, Chen RF, Yen CT. Dynamic changes of touch- and laser heat-evoked field potentials of primary somatosensory cortex in awake and pentobarbital-anesthetized rats. *Brain Res* 2001; **911**: 105–15

99 Shimoji K, Bickford RG. Differential effects of anesthetics on mesencephalic reticular neurons. I. Spontaneous firing patterns. *Anesthesiology* 1971; **35**: 68–75

100 Shimoji K, Matsuki M, Shimizu H, Maruyama Y, Aida S. Dishabituation of mesencephalic reticular neurons by anesthetics. *Anesthesiology* 1977; **47**: 349–52

101 Shimoji K, Fujioka H, Fukazawa T, Hashiba M, Maruyama Y. Anesthetics and excitatory/inhibitory responses of midbrain reticular neurons. *Anesthesiology* 1984; **61**: 151–5

102 Shimoji K, Fujioka H, Ebata T. Anesthetics block excitation with various effects on inhibition in MRF neurons. *Brain Res* 1984; **295**: 190–3

103 Simone DA, Hanson ME, Bernau NA, Pubols BH,jr. Nociceptive neurons of the raccoon lateral thalamus. *J Neurophysiol* 1993; **69**: 318–28

104 Sparks DL, Corssen G, Aizenman B, Black J. Further studies of the neural mechanisms of ketamine-induced anesthesia in the rhesus monkey. *Anesth Analg* 1975; **54**: 189–95

105 Steinfels GF, Heym J, Strecker RE, Jacobs BL. Behavioral correlates of dopaminergic unit activity in freely moving cats. *Brain Res* 1983; **258**: 217–28

106 Stone JL, Ghaly RF, Levy WJ, Kartha R, Krinsky L, Roccaforte P. A comparative analysis of enflurane anesthesia on primate motor and somatosensory evoked potentials. *Electroencephalogr Clin Neurophysiol* 1992; **84**: 180–7

107 Stucke AG, Stuth EA, Tonkovic-Capin V, *et al*. Effects of sevoflurane on excitatory neurotransmission to medullary expiratory neurons and on phrenic nerve activity in a decerebrate dog model. *Anesthesiology* 2001; **95**: 485–91

108 Stuth EA, Krolo M, Tonkovic-Capin M, Hopp FA, Kampine JP, Zuperku EJ. Effects of halothane on synaptic neurotransmission to medullary expiratory neurons in the ventral respiratory group of dogs. *Anesthesiology* 1999; **91**: 804–14

109 Stuth EA, Krolo M, Stucke AG, *et al*. Effects of halothane on excitatory neurotransmission to medullary expiratory neurons in a decerebrate dog model. *Anesthesiology* 2000; **93**: 1474–81

110 Sudo M, Sudo S, Chen XG, Piercy M, Carstens E, Antognini JF. Thiopental directly depresses lumbar dorsal horn neuronal responses to noxious mechanical stimulation in goats. *Acta Anaesthesiol Scand* 2001; **45**: 823–9

111 Toyooka H, Kitahata LM, Dohi S, Ohtani M, Hanaoka K, Taub A. Effects of morphine on the rexed lamina VII spinal neuronal

response to graded noxious radiant heat stimulation. *Exp Neurol* 1978; **62**: 146–58

112 Tsoukatos J, Kiss ZH, Davis KD, Tasker RR, Dostrovsky JO. Patterns of neuronal firing in the human lateral thalamus during sleep and wakefulness. *Exp Brain Res* 1997; **113**: 273–82

113 Uchida H, Kishikawa K, Collins JG. Effect of propofol on spinal dorsal horn neurons. Comparison with lack of ketamine effects. *Anesthesiology* 1995; **83**: 1312–22

114 Urban BW, Friederich P. Anesthetic mechanisms in-vitro and in general anesthesia. *Toxicol Lett* 1998; **100/101**: 9–16

115 Vahle-Hinz C, Hicks TP, Gottschaldt KM. Amino acids modify thalamo-cortical response transformation expressed by neurons of the ventrobasal complex. *Brain Res* 1994; **637**: 139–55

116 Vahle-Hinz C, Detsch O, Siemers M, Kochs E, Bromm B. Local GABA(A) receptor blockade reverses isoflurane's suppressive effects on thalamic neurons *in vivo*. *Anesth Analg* 2001; **92**: 1578–84

117 Vahle-Hinz C, Reeker W, Detsch O, Siemers M, Kochs E, Bromm B. Antinociceptive effects of anesthetics *in vivo*: thalamic neuronal responses and cellular mechanisms. In: Urban BW, Barann M, eds. *Molecular and Basic Mechanisms of Anesthesia*. Berlin: Pabst Scientific Publishers, 2002; in press

118 Veselis RA, Reinsel RA, Feshchenko VA. Drug-induced amnesia is a separate phenomenon from sedation: electrophysiologic evidence. *Anesthesiology* 2001; **95**: 896–907

119 Wall PD. The laminar organization of dorsal horn and effects of descending impulses. *J Physiol* 1967; **188**: 403–23

120 Webb AC. Consciousness and the cerebral cortex. *Br J Anaesth* 1983; **55**: 209–19

121 West MO. Anesthetics eliminate somatosensory-evoked discharges of neurons in the somatotopically organized sensorimotor striatum of the rat. *J Neurosci* 1998; **18**: 9055–68

122 Wolstencroft JH, West DC. Functional characteristics of raphe spinal and other projections from nucleus raphe magnus. In: Sjölund B, Bjorklund A, eds. *Brain Stem Control of Spinal Mechanism*. Oxford: Elsevier, 1982: 359–80

123 Yaksh TL. Pharmacology and mechanisms of opioid analgesic activity. *Acta Anaesthesiol Scand* 1997; **41**: 94–111

124 Yamamori Y, Kishikawa K, Collins JG. Halothane effects on low-threshold receptive field size of rat spinal dorsal horn neurons appear to be independent of supraspinal modulatory systems. *Brain Res* 1995; **702**: 162–8

125 Yamamoto M, Nakahama H, Shima K, Kodama T, Mushiake H. Markov-dependency and spectral analyses on spike-counts in mesencephalic reticular neurons during sleep and attentive states. *Brain Res* 1986; **366**: 279–89

126 Yanagidani T, Ota K, Collins JG. Complex effects of general anesthesia on sensory processing in the spinal dorsal horn. *Brain Res* 1998; **812**: 301–4

127 Zhang Y, Eger EI, Dutton RC, Sonner JM. Inhaled anesthetics have hyperalgesic effects at 0.1 minimum alveolar anesthetic concentration. *Anesth Analg* 2000; **91**: 462–6

128 Zurita P, Villa AE, de Ribaupierre Y, de Ribaupierre F, Rouiller EM. Changes of single unit activity in the cat's auditory thalamus and cortex associated to different anesthetic conditions. *Neurosci Res* 1994; **19**: 303–16