Anaesthesia and PET of the Brain

Absalom, Anthony; Adapa, Ram

Published in:
PET and SPECT in Neurology

DOI:
10.1007/978-3-030-53168-3_44

Publication date:
2020

Anaesthesia and PET of the Brain

44

Anthony Absalom and Ram Adapa

Contents

Abstract

Although drugs have been used to administer general anaesthesia for more than a century and a half, relatively little was known until recently about the molecular and cellular effects of the anaesthetic agents and the neurobiology of anaes-

A. Absalom (✉)
Department of Anesthesiology, University Medical Center Groningen, Groningen University, Groningen, The Netherlands
e-mail: a.r.absalom@umcg.nl

R. Adapa
Anaesthetic Department, Addenbrooke's Hospital, Cambridge, UK
e-mail: ra342@cam.ac.uk

R. A. J. O. Dierckx et al. (eds.), *PET and SPECT in Neurology*,
https://doi.org/10.1007/978-3-030-53168-3_44

thesia. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies have played a valuable role in improving this knowledge. PET studies using ^{11}C-flumazenil binding have been used to demonstrate that the molecular action of some, but not all, of the current anaesthetic agents is mediated via the $GABA_A$ receptor. Using different tracers labelled with ^{18}F, ^{11}C and ^{15}O, PET studies have shown the patterns of changes in cerebral metabolism and blood flow associated with different intravenous and volatile anaesthetic agents. Within classes of volatile agents, there are minor variations in patterns. More profound differences are found between classes of agents. Interestingly, all agents cause alterations in the blood flow and metabolism of the thalamus, providing strong support for the hypothesis that the anaesthetic agents interfere with consciousness by interfering with thalamocortical communication.

44.1 Introduction

Every day, around the world, a large number of patients receive sedative and anaesthetic agents for sedation and anaesthesia in intensive care units, in operating theatres and in other centres where diagnostic and therapeutic procedures are performed. Despite this and the fact that anaesthetic drugs have been used regularly since the 1840s, surprisingly, little is known about the state of anaesthesia, the mechanism and site of action of the anaesthetic agents and the longer-term consequences of sedation and anaesthesia. In the early 1990s, so little was known about the state of anaesthesia that Christof Koch co-wrote a serious article discussing the basic question 'Does anaesthesia cause loss of consciousness?' (Kulli and Koch 1991). In the decades since, significant progress has been made, thanks mostly to developments in technologies for functional imaging, such as PET, but still many fundamental questions remain unanswered! Part of the reason for slow progress is the current limited understanding of the neurobiology of consciousness.

Although anaesthesia is sometimes required for clinical PET scanning of the brain and other organs, the anaesthetic management of patients undergoing scanning will not be discussed here. Rather, this chapter will focus on the application of PET brain scanning techniques to studies of the neurobiology of anaesthesia.

44.2 Consciousness and Unconsciousness

One of the aims of anaesthesia is to induce loss of consciousness and prevent return of consciousness during a surgical procedure. Consciousness is an ethereal concept, whose nature and meaning have been debated for centuries. Today, most people believe it to be a subjective experience resulting from the electrical activity of the neurons in the brain (or more accurately the co-ordinated activity of assemblies or networks of neurons). Generally, we infer that an individual is conscious on the

basis of his behaviour, his interactions with his environment and his reports of his experiences.

Medically, we define unconsciousness as an absence of wakefulness, alertness and awareness, but inferences that these are absent are usually based on the absence of behavioural responses to external stimuli. There are several circumstances when such inferences may not be true, as in patients with the 'locked-in' syndrome. In anaesthetic practice, we commonly administer doses of opioid drugs that obtund responses to stimuli (but do not necessarily by themselves prevent consciousness), and in patients presumed to be unconscious, we often administer drugs that paralyze the muscles but do not alter consciousness.

The literature contains a wide range of published incidences of the so-called problem of accidental awareness of general anaesthesia with subsequent recall of intraoperative events (AAGA). The differences arise mostly from differences in study population and methodology. The reported incidence also appears to be higher when structured postoperative interviews are used to test for explicit recall (Mashour et al. 2013; Walker et al. 2016), with incidences in large trials of the 1–2 out of every 1000 patients undergoing anaesthesia (Sandin et al. 2000; Sebel et al. 2004). A recent large UK national audit project (NAP5) indicated that the incidence of spontaneous complaints of AAGA is much lower (~1: 19,000 patients) but higher in specific patient populations and a wide range of psychological consequences (Pandit et al. 2014). The incidence of awareness during surgery without subsequent recall is not known but is likely to be much higher (Absalom and Green 2013).

44.3 Definition of Anaesthesia

Due to the combined problems of a poor understanding of consciousness and of the effects of anaesthetic drugs on the brain, anaesthesia has been very difficult to define and has largely been defined on the basis of the absence of features of consciousness. For most of the history of the practice of anaesthesia, anaesthesiologists have tended to define adequate clinical anaesthesia as a triad of 'hypnosis', analgesia and muscle relaxation. In anaesthetic jargon, anaesthetic-induced loss of consciousness is referred to as 'hypnosis' and anaesthesia-inducing drugs as 'hypnotics'. The term 'analgesia' was previously used to refer more generally to the (desired) loss of autonomic responses to painful stimuli, and muscle relaxation referred to the desire of the surgeon for a lack of patient movement and for some operations a reduction in muscle tone. Early volatile anaesthetic agents were able to suppress consciousness and, in sufficiently large doses, were able to suppress autonomic responses (tachycardia, hypertension) and reduce muscular tone. These latter effects are mediated by separate actions of the drugs on different parts of the nervous system and on the cardiovascular system and are not part of a single spectrum of effects at a single site (Prys-Roberts 1987; Kissin 1993). Thus, modern clinical practice involves administration of different 'purer' agents targeted at different elements of this triad—modest doses of hypnotic agents for suppression of consciousness, local and systemic analgesic drugs for suppression of autonomic responses and neuromuscular

blocking agents for muscle relaxation or paralysis where that is required. With this approach, more attention is now focused on the cognitive aspects of anaesthesia, with anaesthesia being defined as a drug-induced reversible state of unconsciousness principally characterized by a lack of awareness of, and subsequent memory for, intraoperative events.

Thus, this chapter will focus on the use of PET technology to understand the main component of anaesthesia, 'hypnosis', and will not deal with functional imaging of pain perception and analgesia.

44.4 Why Study Anaesthesia?

In current clinical practice, many anaesthesiologists err on the side of deeper anaesthesia in the hope of avoiding the problem of anaesthetic awareness. This is not an ideal approach since all the anaesthetic agents in current use possess dose-related adverse effects, such as depression of the cardiovascular and immune systems.

Earlier studies suggested an association between excessive depth of anaesthesia (i.e. an excessive dose) and mortality within 1 and 2 years (Monk et al. 2005; Lindholm et al. 2009). A recent large randomized controlled trial however indicated that there was no difference in 1-year mortality between light general anaesthesia and deep general anaesthesia in elderly patients (Short et al. 2019).

Animal evidence suggests that in the extremes of age (i.e. in the very young and the elderly), anaesthetic agents may be neurotoxic.

There is a plethora of evidence that exposure of a wide variety of animals to the commonly used anaesthetic agents during the neonatal period results in neuronal injury and associated cognitive changes (Jevtovic-Todorovic et al. 2013). Epidemiological studies of neonatal exposure to anaesthetic agents have shown conflicting results, whereas a randomized controlled trial in human neonates showed no evidence of changes in cognitive function at 3 and 5 years after exposure (Davidson et al. 2016; McCann et al. 2019).

While there is some in vitro evidence that anaesthetic agents may promote Alzheimer's disease-type changes (Mandal and Fodale 2009; Whittington et al. 2011), so far, there is no convincing clinical evidence that anaesthetic exposure enhances neurodegenerative processes in the ageing brain.

Studies of the molecular mechanisms of action of the anaesthetic agents offer much more than simply satisfying the curiosity of anaesthesiologists. Better knowledge of the molecular mechanism may inform the development of newer agents, specifically designed to have a broader therapeutic range and fewer adverse effects.

Furthermore, studies of the mechanism of action of the anaesthetic agents may provide information about the nature of, and the mechanisms of, consciousness itself. Here, the hypnotics or sedatives used could be regarded as probes, by which investigators can interfere with different cognitive functions, to help shed light on functions such as speech processing and memory functions (Davis et al. 2007; Adapa et al. 2014; Naci et al. 2018), alertness, wakefulness, awareness and

consciousness itself (Arhem et al. 2003; Lydic and Baghdoyan 2005; Hameroff 2006; Mashour 2006; Franks 2008; Alkire et al. 2008b; Brown et al. 2010; Varley et al. 2019). Once again, this knowledge has practical relevance, since a better understanding of memory function, and of the interactions among anaesthetic agents and stress on awareness and memory function, may inform methods of detecting and preventing inadvertent awareness with subsequent recall of intraoperative events.

44.5 Available Tools for Studying Anaesthesia

To fully understand anaesthesia, multiple layers and domains of knowledge are required, starting with the molecular effects (or possibly at submolecular level), explaining how these influence the function of individual neurons and how these influence the interactions or communication among networks or assemblies of other neurons, before making the jump to explain how the perturbed electrical and other activities in these assemblies or networks of neurons eventually result in impairment or absence of consciousness.

Different techniques lend themselves to study of different parts of this chain of events. Molecular biology laboratory techniques (such as identification and isolation of specific receptor types and patch-clamp techniques to measure the effects of ion fluxes in response to application of different agonists and antagonists) have been the basis for much of our improved understanding of the molecular actions of our agents. However, as will be seen below, in recent years, PET-based techniques have also been used to study receptor effects.

Cellular function is also commonly studied by molecular biology techniques and by recordings of local field potentials, usually in animals (Imas et al. 2006). PET techniques have been used very successfully to describe the indirect neurophysiological effects of anaesthetic agents such as changes in regional blood flow and metabolism secondary to changes in neuronal (electrical) activity. Occasionally, clever designs have been used to link these regional changes with specific neuronal populations.

Changes in regional neurophysiology are also detectable with functional MRI techniques, in which the scanner sequences are chosen so that regional changes in blood oxyhaemoglobin levels are detectable. This so-called BOLD or blood oxygen level-dependent signal relies on the fact that deoxyhaemoglobin is paramagnetic, whereas oxyhaemoglobin is not. When regional neuronal electrical activity increases, local blood flow and oxygen delivery increase in excess of the increase in oxygen requirements, thereby causing a reduction in the regional concentration of deoxyhaemoglobin and the MRI signal. These fMRI techniques have the benefit of superior temporal resolution compared with PET but suffer from the disadvantage of worse spatial resolution. There is also sometimes debate about the validity of fMRI techniques when anaesthetic agents are used, since, although the anaesthetic agents generally cause matched reductions in cerebral electrical activity,

metabolism and flow, they can also have direct vasodilatory effects which result in oxygen delivery in excess of requirements and thus produce BOLD signal changes unrelated to changes in neuronal activity.

We assume that cognitive functions are mediated by electrical activity in networks of neurons, and so perhaps electroencephalography (EEG) can be said to be the most direct and objective measure of brain activity. It has excellent temporal resolution but only reflects cortical activity and represents the summed activity of millions of cortical pyramidal neurons in the vicinity of each electrode. Nonetheless, EEG-based monitors of anaesthetic depth have been developed and shown to assist with rational and patient-individualized titration of anaesthetic dose. These monitoring techniques suffer from the disadvantage that at best, their output correlates with the probability of consciousness but seldom gives an absolute indication of whether consciousness is present or absent. Although there are EEG patterns associated with wakefulness and also with very deep anaesthesia, there is currently no known EEG signal that can clearly detect the transition between consciousness and unconsciousness. Some early efforts have been made to integrate information obtained from electroencephalography with that from PET-based assessments of changes in regional neurophysiology (Noirhomme et al. 2009). Others have combined transcranial magnetic stimulation and EEG recording to yield insights into differences in signal transmission during wakefulness and natural sleep (Massimini et al. 2005, 2007). Finally, studies of the regional correlations in electrical activity, and in particular coherence analyses, are beginning to yield interesting insights into how anaesthetic agents might interfere with the transfer of information between regions (Lee et al. 2009).

Ultimately though, the aim of anaesthesia is to induce loss of consciousness and prevent return of consciousness during a surgical procedure. To understand how the molecular, cellular and neuronal network effects of the anaesthetic agents finally result in a change of consciousness and memory functions is possibly the most challenging step, since it remains to be explained how molecular, cellular and electrical activity generates conscious experiences at all.

In anaesthetic studies, a common aim is to correlate drug-induced regional neurophysiological changes with cognitive function changes. This can be difficult to achieve, even with the time-honoured behavioural testing techniques of cognitive neuroscience and experimental psychology. At lower, sedative doses, when some cognitive functions are still intact, behavioural and memory testing is informative. However, when the end point is loss of consciousness, observations of behaviour and memory are only partially informative. Firstly, assessment of behavioural responses usually involves application of a verbal or painful stimulus that may itself alter the state of consciousness. Secondly, the absence of behavioural responses does not always imply lack of consciousness, but may only indicate a failure of volition or motor control, and in some circumstances, movement in response to pain can occur without the presence of consciousness. Likewise, reliance on explicit memory is not always informative, since sub-sedative doses of several anaesthetic agents are associated with profound amnesia.

44.6 Early Theories of the Molecular Mechanism of Anaesthetic Action

The range of possible types of theories for the mechanism of action is from so-called unitary theories, proposing a single neuronal target, to hypotheses that propose multiple neuronal targets per drug. For most of the twentieth century, the Meyer-Overton hypothesis—a unitary theory—held sway. It was noted that the potency of the anaesthetic agents correlated with their lipid solubility, and this combined with the observation that increases in ambient pressure could reverse anaesthesia leads to the conclusion that anaesthetic effects were mediated by a non-specific physical effect on the lipid bilayer of neuronal cell membranes. It was thought that the physical presence of anaesthetic molecules within this layer caused alterations in membrane volume and fluidity, resulting in dose-dependent dysfunction of all exposed neurons.

Towards the end of the twentieth century, evidence mounted against the Meyer-Overton hypothesis. Studies showed that membrane volume changes were in fact negligible. Other evidence against a non-specific mechanism came from increasing knowledge of exceptions to the rule and biochemical experiments with known anaesthetic agents where small alterations in structure were associated with loss of anaesthetic potency. Further evidence against a simple physical mechanism came from studies showing that current flows along giant squid axons (mediated by voltage-gated Na and K channels) were insensitive to anaesthetic agents (Haydon and Urban 1983, 1986). A major breakthrough came when Franks and Lieb produced the first strong evidence that known anaesthetic agents exhibited dose-dependent effects on proteins, leading to the suggestion that anaesthetic agents acted on membrane receptors (Franks and Lieb 1984). Nonetheless, the academic community was slow to accept this, and it was only with growing evidence against non-specific membrane effects (such as the demonstration of differences in potency among optical isomers of known anaesthetic agents (Franks and Lieb 1993)) and growing evidence of specific effects at receptors (Hales and Lambert 1991; Franks and Lieb 1997) that the Meyer-Overton hypothesis was gradually rejected.

44.7 Current Theories of the Molecular Mechanism of Anaesthetic Action

Most workers in the field now agree that anaesthetic agents act to hyperpolarize neurons by either potentiating inhibitory circuits or inhibiting excitatory pathways and that they do so by specific actions at ligand-gated receptors (Franks 2008; Alkire et al. 2008b; Franks and Lieb 2004). In the case of the commonly used intravenous anaesthetic agent propofol, and for the less commonly used agents such as the barbiturates and etomidate, the chief molecular effect seems to be potentiation at the $GABA_A$ receptor. Gene knockout studies in animals suggest that the different components of the clinical effects of these agents, such as amnesia and sedation, are

mediated by different $GABA_A$ receptor subtypes. In fact, sensitivity to the different anaesthetic effects may be strongly modulated by single nucleotide substitutions (Belelli et al. 1997; Mihic et al. 1997; Reynolds et al. 2003), suggesting a potential genetic basis for some of the pharmacodynamic variability seen in clinical practice. Although the $GABA_A$ receptor is posited to be the main molecular site of action, there is also evidence for effects at an array of other sites, such as at nicotinic ACh receptors and voltage-gated potassium channels, although the significance of these effects is unclear (Fig. 44.1).

Two less commonly used intravenous anaesthetic agents that have not yet been mentioned are ketamine and dexmedetomidine. Ketamine causes potent analgesia, and when used as the sole hypnotic, it causes a dissociated state (in which the patient may appear conscious but is dissociated from the environment and applied stimuli). Both effects are mediated via an antagonist effect at the NMDA glutamate receptor (Franks 2008; Alkire et al. 2008b). Dexmedetomidine also has some weaker analgesic effects and at low doses causes arousable sedation not dissimilar to a natural sleep state, with general anaesthesia occurring at much higher doses. These effects are mediated by an agonist effect at α2 adrenergic receptors, with sedative and hypnotic effects probably mediated by actions on these receptors in the locus coeruleus.

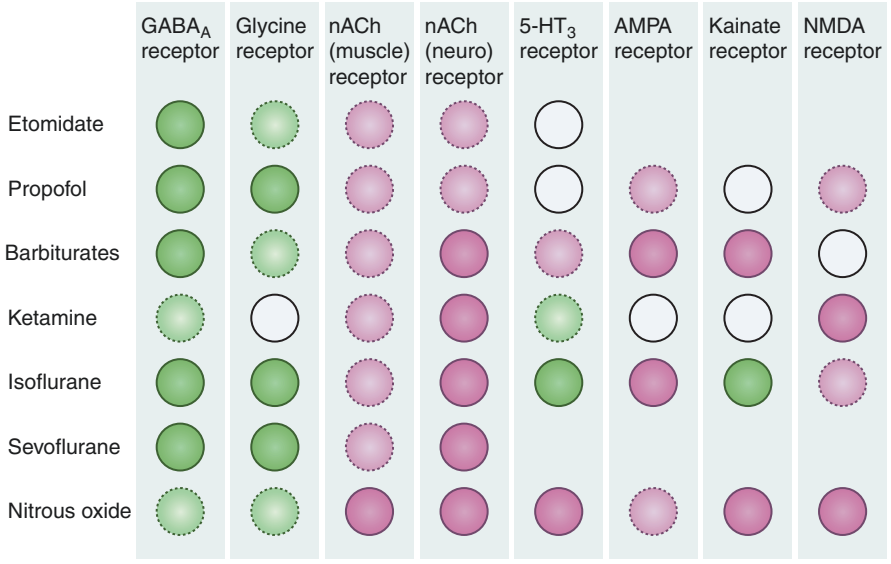

Fig. 44.1 Ligand-gated ion channels are probably the most relevant targets for general anaesthetics. A *dark green* or *pink spot* indicates significant potentiation or inhibition, respectively, of agonist actions at the receptor by the anaesthetic with an *EC50* or *IC50* that is no greater than three times higher than the EC50 for producing immobility. A *light green* or *light pink spot* indicates little potentiation or inhibition, respectively, at concentrations that were less than three times the EC50 for immobility; an *empty spot* indicates no effect at any concentration tested. (From Rudolph and Antkowiak (2004) used with permission)

For the volatile anaesthetic agents, agonist effects at the $GABA_A$ receptor appear to be important (Alkire et al. 2008b) but with binding of the agents to different binding sites than those for propofol and the barbiturates. The molecular mechanism of action of the volatile agents may also include significant potentiating effects at two-pore potassium and glycine channels and inhibitory effects at NMDA receptors (Franks 2008).

44.8 Early PET Studies of the Global and Regional Changes in Cerebral Glucose Metabolism Caused by Anaesthetic Agents

The earliest PET studies of anaesthesia were performed in rats, in which ^{18}FDG was used during propofol anaesthesia, and showed dose-dependent global reductions in cerebral glucose utilization (Ori et al. 1986; Dam et al. 1990; Cavazzuti et al. 1991). These studies led Dr Michael Alkire to perform the first PET studies of anaesthesia in humans. In that, ^{18}FDG was used before and during propofol anaesthesia, and as in the rat studies, it was found that anaesthesia caused reductions in glucose metabolism in all measured cortical and subcortical areas (Alkire et al. 1995). In this study, marked regional differences in tracer uptake were noted, with a greater suppression of cortical than subcortical activity. At this time, it was just becoming apparent that the molecular mechanism of action of propofol was mediated by the $GABA_A$ receptor. These regional differences even led Alkire and colleagues to speculate that differences in the regional distribution of $GABA_A$ receptors were responsible for the regional variations in metabolic activity.

Alkire and his group then went on to study the influence of isoflurane anaesthesia on glucose metabolism, again using the ^{18}FDG tracer (Alkire et al. 1997). Although they found a similar degree of global reduction in metabolic activity to propofol, they found less regional variability with isoflurane. They found similar reductions in cortical and subcortical activity and widespread, fairly uniform reductions in activity across all cortical and subcortical areas. This widely quoted study was taken to provide support for a non-specific, physical explanation of the mechanism of action of the anaesthetic agents.

A subsequent study with an older volatile anaesthetic agent, halothane, showed similar global reductions in metabolic activity to isoflurane and propofol (40% vs. 46% and 55%, respectively) (Alkire et al. 1999). In general, the pattern of regional metabolic effects was similar to that found with isoflurane, with the exception of the cerebellum, where metabolism was more suppressed by halothane. As with isoflurane, midbrain metabolism was more suppressed than with propofol, and here, the authors speculated that this is because the volatile anaesthetics have a strong influence on cholinergic transmission, whereas propofol does not.

Each of the above three studies involved only a small number of subjects, in whom anaesthetic dose was titrated to loss of consciousness, with concurrent EEG monitoring, using the bispectral index (BIS) monitor (Covidien, USA), a monitor of depth of anaesthesia, which gives an output of between 0 and 100, where zero

indicates no brain electrical activity and 100 the completely awake state and values between 40 and 60 are taken to represent adequate anaesthesia. The authors combined the data to show that the degree of global reduction in glucose metabolism correlated strongly with the bispectral index (Alkire 1998).

Although the above findings were sometimes taken to provide evidence of a non-specific mechanism of anaesthetic activity, they also indicated differences between anaesthetic agents and regional variations in metabolic suppression, providing evidence against the theory of a single non-specific mechanism of action. In the subsequent years, the evidence against this theory continued to mount up, particularly as investigators designed more sophisticated studies, combined imaging modalities and compared the results of different drugs and modalities. PET methodology played an important role in this. Indeed, by 2005, there was sufficient evidence from studies involving PET measures of cerebral blood flow and metabolism with different anaesthetic agents for Alkire to perform a conjunction analysis. This analysis highlighted the considerable regional differences among different agents, thereby providing strong evidence for specific anaesthetic effects (Alkire and Miller 2005). Further, despite differences in molecular mechanisms and in regional neurophysiological effects, all agents with anaesthetic effects had in common a significant effect on the thalamus (see Fig. 44.2). Based on this work and on previous animal findings (Angel 1993), Alkire became a strong proponent of the 'thalamocortical switch hypothesis', the theory that thalamocortical resonant loops are essential for consciousness and that all anaesthetic agents interrupt consciousness by interrupting the thalamocortical interactions and interrupting onward transmission of ascending electrical signals (Alkire et al. 2000).

Subsequent work using PET has assessed various combinations of cerebral metabolism, blood flow, blood volume and receptor occupancy, for different drugs (sometimes in combination). To simplify the findings, they will be subdivided by drug type, starting with the intravenous agents (propofol, ketamine and the alpha2 agonists) and finishing with the inhaled agents (volatile anaesthetic agents, nitrous oxide, xenon).

44.9 PET and Propofol

The early work by Alkire et al. (1995) has already been mentioned. Although this showed global reductions in glucose metabolism, the effects of propofol on relative glucose metabolism were different for different areas (where regional metabolism as a proportion of global metabolism is considered). Thus, whereas the relative glucose metabolism decreased for most cortical areas and the thalamus, there were relative increases for the temporal lobe, hippocampus, basal ganglia, midbrain and cerebellum.

Fiset and colleagues used $H_2{}^{15}O$ PET to study changes in global and regional cerebral blood flow (rCBF) associated with mild sedation, deep sedation and unconsciousness induced by propofol (Fiset et al. 1999). Concordant with the findings of Alkire, they found dose-related decreases in global CBF. Further, they identified

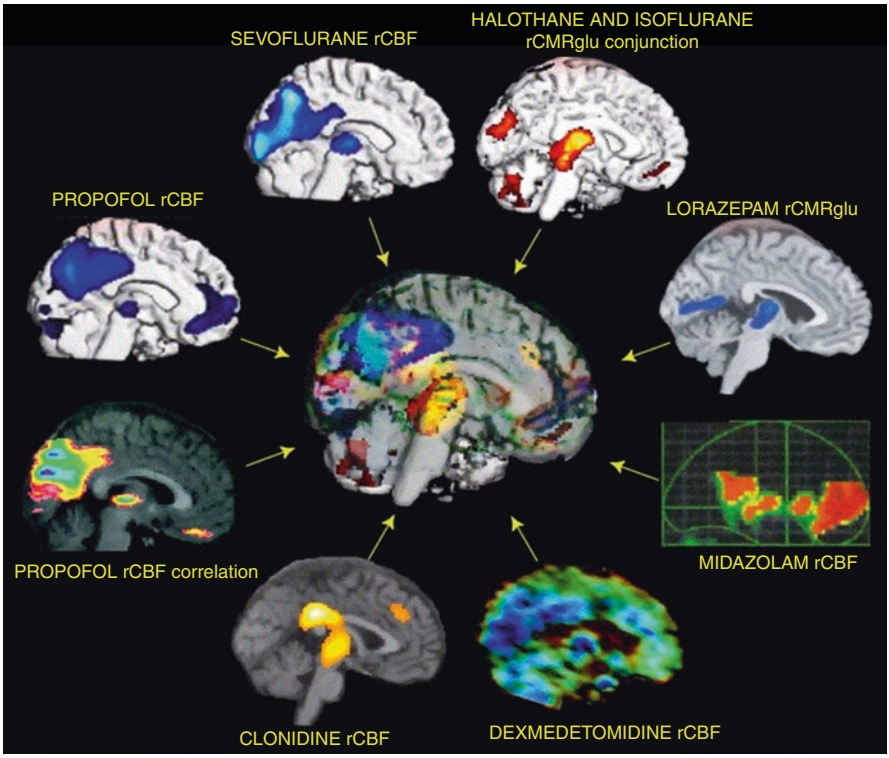

Fig. 44.2 The regional effects of anaesthetics on brain function in humans who were given various anaesthetic agents at doses that altered the level of consciousness. The data are from seven different groups of investigators and encompass the study of eight different agents. The regional effects were measured using blood-flow- or glucose-metabolism-based techniques. All images show regional decreases in activity caused by anaesthesia compared to the awake state, except the propofol correlation image, which shows increasing anaesthetic dose correlates with decreasing blood flow. The figure identifies that altered blood flow and metabolism in the thalamus are a common finding associated with anaesthetic-induced unconsciousness. (From Alkire and Miller (2005) used with permission)

evidence supporting specific molecular effects of propofol. They found that propofol preferentially decreased rCBF in brain regions involved in arousal, autonomic functions and associative functions, such as the medial thalamus, midbrain, cuneus and precuneus, posterior cingulate cortex and orbitofrontal regions. Interestingly, there were strong correlations in rCBF in the midbrain and thalamus, indicating strong functional interactions between the arousal systems of these regions.

In a more sophisticated study, this group measured CBF responses (using $H_2{}^{15}O$ PET) to vibrotactile stimulation during graded sedation and anaesthesia (Bonhomme et al. 2001). In general, this study demonstrated that propofol caused dose-dependent decreases in rCBF in the thalamus, bilateral precuneus and bilateral posterior cingulate gyri. During unconsciousness, there were widespread increases in rCBF when $PaCO_2$ was increased by 20%, which can be explained by the fact that CO_2

reactivity is preserved with propofol. In the awake state, vibrotactile stimulation produced a predicted pattern of rCBF changes—increases in relative rCBF in the left thalamus and primary somatosensory cortex (S1) and left superior frontal gyrus and bilateral secondary somatosensory (S2) cortices. Most interesting was the finding that propofol produced dose-dependent, selective regional effects on the responses to vibrotactile stimulation. At low sedative doses, the S1 responses were abolished, and at moderate sedative doses, the S2 responses were abolished (and accompanied by changes in sensory perception), whereas thalamic responses were only abolished when consciousness was lost.

Scheinin et al. in Finland used $H_2{}^{15}O$ PET to assess changes in absolute and relative CBF during graded general anaesthesia (from moderate to deep levels) with propofol and sevoflurane (Kaisti et al. 2002). Propofol caused a significant global decrease in absolute rCBF but with a ceiling effect at the lowest anaesthetic concentration studied (a target plasma concentration of 6 μg/mL, which is approximately the concentration required to suppress movement responses to pain in 50% of patients). The transition from the awake state to that at EC50 was associated with relative rCBF decreases in the thalamus, midbrain, cuneus, precuneus, posterior limbic system and parietal and frontal cortices. The lack of absolute changes in rCBF with propofol, even at 2 × EC50, suggested that flow-metabolism coupling is maintained during propofol anaesthesia. In a subsequent study by the same group, also involving propofol anaesthesia, but at a lower dose (mean measured concentration 3.7 μg/mL), similar changes in rCBF, regional oxygen metabolism and regional cerebral blood volume (assessed by $H_2{}^{15}O$, $^{15}O_2$ and $C_{15}O$ tracers, respectively) were found (Kaisti et al. 2003). This provided evidence of intact flow-metabolism coupling at this low dose, which suggests that low-dose propofol anaesthesia does not produce direct vasodilatory effects. Another group administered a similar level of propofol anaesthesia (targeting a BIS of 35–40) to volunteers and found similarly matched changes in flow and metabolism (in this case, metabolism was assessed with ^{18}FDG PET) (Schlunzen et al. 2012).

Most studies of the influence of propofol metabolism have assessed glucose or oxygen metabolism. One study, however, has assessed regional cerebral protein synthesis rates using the tracer L-[1-^{11}C]leucine (Bishu et al. 2009). No effect of propofol on protein synthesis was found (measured propofol concentrations were in the range 4.2–8.1 μg/mL).

The remaining studies to be discussed in this section were focused on receptor effects of propofol. Alkire and Haier performed a study in which they correlated their findings concerning regional cerebral glucose metabolism rates under propofol and isoflurane anaesthesia, with data previously published by other investigators on the regional distributions of different neurotransmitter systems (Alkire and Haier 2001). The latter data were acquired from post-mortem immunochemistry investigations (Braestrup et al. 1977; Zezula et al. 1988; Enna and Snyder 1977). They were able to show that there were significant correlations between regional reductions in glucose metabolism during propofol anaesthesia and the regional distribution of benzodiazepine binding sites (from studies using ^{3}H-diazepam which binds to both neuronal and mitochondrial benzodiazepine receptors and ^{3}H-flunitrazepam

which binds only to neuronal benzodiazepine binding sites on $GABA_A$ receptors). There were also weaker correlations with the distribution of opioid binding sites but no correlations with distribution densities of adrenergic, muscarinic and serotonin binding sites.

Salmi and colleagues later showed that propofol increases ^{11}C-flumazenil binding, indicating that propofol enhances the affinity of GABA for $GABA_A$ receptors (Salmi et al. 2004). At around the same time, another group found that propofol anaesthesia was associated with a reduction in muscarinic receptor binding by the tracer [*N*-^{11}C-methyl]-benztropine (Xie et al. 2004), but this finding was difficult to interpret. Although it may have indicated binding of propofol to muscarinic receptors, it could also have been the result of a change of affinity of the receptor for benztropine or an increase in benztropine metabolism caused by propofol. Several years later, members of the same group performed an intriguing study in which they measured CBF with a $H_2{}^{15}O$ technique at baseline, after loss of consciousness with propofol and administration of the cholinesterase inhibitor, physostigmine (Xie et al. 2011). Some, but not all, volunteers regained consciousness after physostigmine administration, despite constant blood and brain concentrations of propofol. The authors found that loss of consciousness was associated with decreases in rCBF in the thalamus and precuneus and that among those that regained consciousness after physostigmine, restoration of consciousness was associated with increases in rCBF in these same structures. It is assumed that the increased ACh levels caused by physostigmine result in activation of cholinergic pathways and an increase in thalamic throughput of electrical signals sufficient to cause a return of consciousness.

Taken together, these studies indicate that propofol causes a specific pattern of changes in regional metabolic activity and CBF but with a key effect at the thalamus and that loss of consciousness is associated with interruption of thalamocortical signalling. Finally, the work from the past decade and a half supports the hypothesis that propofol acts at specific protein targets, most notably at the $GABA_A$ receptor.

44.10 PET and Ketamine

Ketamine is an older anaesthetic agent than propofol but is seldom used alone for inducing or maintaining surgical anaesthesia because of a propensity to cause troublesome psychiatric adverse effects. It remains interesting clinically and is being used with increasing frequency as an adjunct during propofol anaesthesia. Known and potential beneficial effects include improved cardiovascular stability, neuroprotection, reduced acute post-operative pain, potent antidepressant activity and attenuation of post-operative hyperalgesia and chronic pain.

Ketamine is also of scientific interest because it acts as an antagonist at the NMDA receptor and causes different neurophysiological changes to the other hypnotics. When used alone, it causes impaired consciousness but with cortical electrical activation accompanied by increases in glucose metabolism (Vollenweider et al. 1997) and rCBF. The reasons behind these effects are not clear. The drug antagonizes an excitatory pathway, but presumably, this results in activation of other

excitatory pathways. Impaired consciousness is probably the result of impaired connectivity or communication between regions of the brain important for consciousness.

Långsjö and colleagues studied the effects of sub-anaesthetic doses of **racemic ketamine** on rCBF, regional oxygen metabolism ($rCMRO_2$) and regional cerebral blood volume (rCBV) using the PET tracers $H_2{}^{15}O$, $^{15}O_2$ and C ^{15}O (Långsjö et al. 2003). Ketamine caused global dose-dependent changes in absolute rCBF, with the biggest changes in the anterior cingulate, insula and frontal cortex (areas involved in pain processing) and also in the thalamus and putamen. As expected, mean systemic arterial pressures were increased. There were no significant changes in $rCMRO_2$, and hence, the oxygen extraction fraction was reduced. rCBV was only increased in the frontal cortex. Taken together, these findings were consistent with known behavioural and electrophysiological changes seen with ketamine sedation but did give rise to a suggestion of altered flow-metabolism coupling. The authors performed a follow-up study, this time using ^{18}FDG to assess regional changes in glucose metabolism (rCMRG) associated with sub-sedative racemic ketamine doses (at the highest dose used in the previous study) (Långsjö et al. 2004). Region of interest analyses showed global absolute increases in rCMRG but with the greatest changes in the thalamus and frontal and parietal cortex. Voxel-based analyses showed increases in relative rCMRG in frontal, temporal and parietal cortices. These changes occurred in a similar distribution and magnitude to the rCBF findings of the previous study (Långsjö et al. 2003), suggesting maintenance of flow-metabolism coupling. The authors suggested that the absence of $rCMRO_2$ changes was the result of non-oxidative glucose metabolism in response to ketamine-induced glutamate release. A recent study by Laaksonen and colleagues comparing the effects of dexmedetomidine, propofol and *S*-ketamine also identified no significant changes in rCMRG in the ketamine cohort (Laaksonen et al. 2018).

The Långsjö group also studied the effects of ***S*-ketamine** on cerebral blood flow and metabolism, using a complex study design (Långsjö et al. 2005). $H_2{}^{15}O$ and $^{15}O_2$ scans were performed during one session, at three moments: awake, during low-dose sub-sedative *S*-ketamine administration and during much higher dose of *S*-ketamine anaesthesia. ^{18}FDG scans were performed 3 weeks before the main study and finally also towards the end of the *S*-ketamine anaesthesia. The authors found dose-dependent increases in total CBF and in absolute rCBF in almost all regions studied. During low-dose *S*-ketamine administration, the greatest increases were in the anterior cingulate, whereas at anaesthetic doses, the largest increase (86.5%) was in the insula. At low doses, there were no significant increases in $rCMRO_2$, whereas at anaesthetic doses, $rCMRO_2$ was increased only in the frontal cortex (by 15.7%). During anaesthesia, rCMRG was only increased in the thalamus, and CBV was increased >50%. These findings show that CBF is increased in excess of metabolic needs, suggesting a disturbance of flow-metabolism coupling. While the excess flow may be perceived to be protective, these findings confirmed the long-held views of anaesthesiologists (based on the work of others using different methodologies) that ketamine is not a suitable agent for use during neurosurgery, where the increases in CBF and CBV can cause increased brain volume, increased intracranial pressure and impaired surgical access.

Finally, the same group studied the influence of sub-anaesthetic doses of ketamine on ^{11}C-flumazenil binding (Salmi et al. 2005). They showed no interference in binding, thereby confirming that ketamine has minimal effects on the $GABA_A$ receptor.

The antidepressant effect of ketamine has also been explored using PET scanning in recent years. Using [^{11}C]DASB PET in healthy volunteers, it was demonstrated that the antidepressant effect was not mediated by ketamine binding to the serotonin transporter (Spies et al. 2018). More recently, the radiotracer ^{18}F-FPEB was used to establish that ketamine leads to a downregulation of the metabotropic glutamate receptor 5 (mGluR5) (Holmes et al. 2019). These two studies highlight how PET imaging can be used to probe existing (serotonin reuptake) and novel (mGluR5) treatment targets for psychiatric disorders.

44.11 PET and Alpha2 Agonists

PET technology has only been used a few times to study the alpha2 agonists, among which clonidine and dexmedetomidine are the two agents available for clinical use. Although clonidine has been available for a long time, it has mainly been used intravenously for its antihypertensive effects. More recently, it has been used as a preoperative oral sedative premedication and perioperatively as an intravenous analgesic adjunct. Dexmedetomidine has been in use for almost 20 years in the USA. Initially, it was mostly used for ICU sedation; more recently, it has been used as a sedative during surgical procedures such as awake craniotomy. It was first registered in Europe in late 2011.

Prielipp used $H_2{}^{15}O$ scans to assess the changes in rCBF during and after low and high sedative dose infusions of dexmedetomidine. The agent caused marked reductions in global CBF and also reductions in absolute rCBF in 13 out of 14 regions of interest studied. There were no significant differences in patterns of rCBF between low and high sedative doses. Despite the rapid pharmacokinetics of dexmedetomidine, CBF remained decreased when assessed 30 min after the end of the dexmedetomidine infusion (Prielipp et al. 2002). This reduction of CBF in the absence of concomitant reduction in $CMRO_2$ raised concerns about the potential for cerebral ischaemia with dexmedetomidine. More recently however, the abovementioned comparative study by Laaksonen et al. revealed that volunteers sedated with dexmedetomidine showed the lowest rCMRG in almost all brain regions compared to other anaesthetics (Fig. 44.3).

More recent reports have studied healthy volunteers sedated with dexmedetomidine in an attempt to explore disruptions in brain functional connectivity with combined PET-fMRI studies. Unconsciousness was associated with reduced regional blood flow and CMRG in the thalamus, the default mode network (DMN) and the bilateral frontoparietal networks (FPNs) (Akeju et al. 2014). Importantly, functional connectivity within these networks was preserved, while internetwork connectivity was disrupted. As reported above, recovery from unconsciousness was associated with sustained reduction in CBF and restored DMN thalamocortical functional connectivity. Other studies have identified greater functional connectivity between the

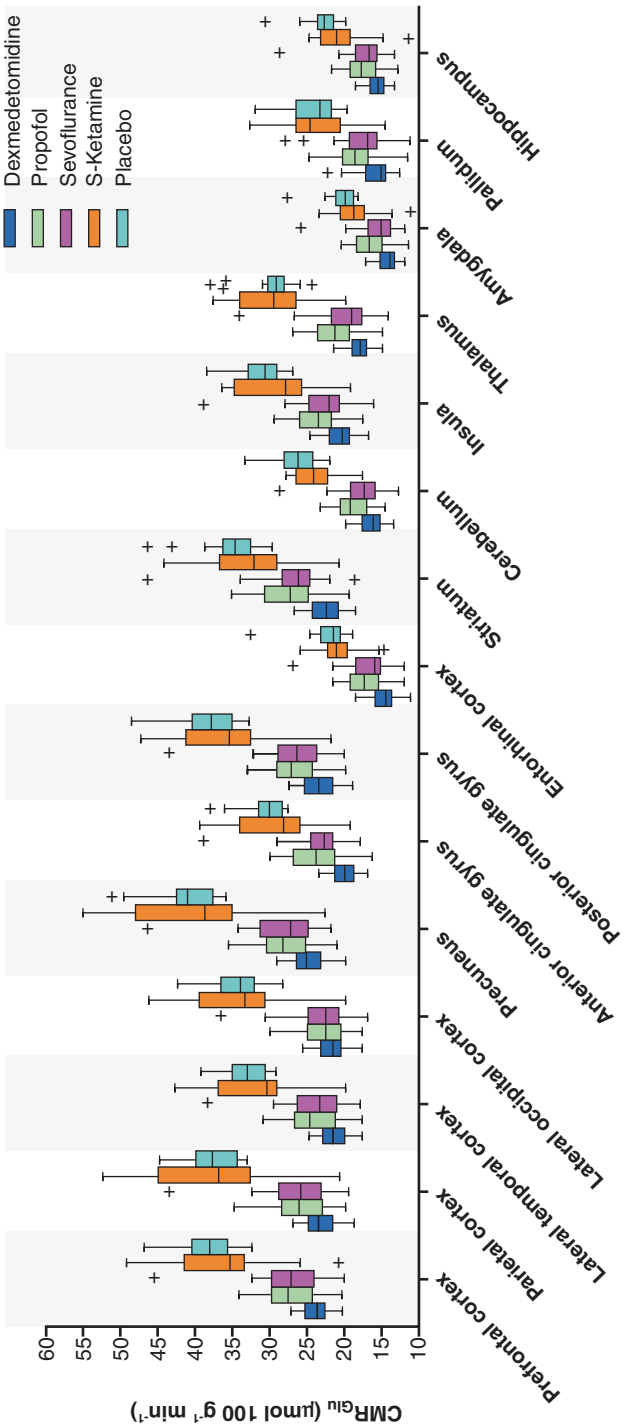

Fig. 44.3 Boxplots of regional cerebral metabolic rate of glucose (CMR_{glu}) in the 15 analyzed regions of interest (ROIs) during dexmedetomidine, propofol, sevoflurane, *S*-ketamine and placebo administration in 160 healthy subjects ($P < 0.001$ between the treatments in all ROIs). Lowest CMR_{glu} values were observed in the dexmedetomidine group. Boxes represent lower quartiles and medians and upper quartiles; whiskers represent 1.5 × interquartile ranges below and above the lower and upper quartiles, respectively. Outlying values are marked with symbols

parietal and anterior cingulate cortex upon emergence from anaesthesia, prompting suggestions of a functional network that activates with restored consciousness (Långsjö et al. 2012).

Another group studied the influence of clonidine infusions on rCBF (assessed by $H_2{}^{15}O$ PET), clinical status and EEG (Bonhomme et al. 2008). Clonidine caused rousable sedation and on the EEG spindle patterns similar to those found during non-rapid eye movement sleep. There was a negative correlation between measured plasma clonidine concentration and rCBF in a network of regions including the thalamus, prefrontal cortex, orbital and parietal association cortex, posterior cingulate cortex and precuneus. Changes in these regions are associated with natural sleep. These regions also form part of the default mode network, whose component areas show strong correlations in activity (assessed by fMRI) during the resting state, but not during task performance conditions (Mason et al. 2007; Stamatakis et al. 2010).

44.12 PET and Volatile Anaesthetic Agents

Volatile anaesthetic agents have been the subject of many PET studies. These have mainly focused on the neurophysiological changes in flow and metabolism and have shown generally concordant findings, with only minor variations between studies, possibly related to differences in dose. Minor variations were found according to drug, despite some chemical differences between the agents studied, such as structure, molecular weight, degree of halogenations and water and lipid solubility. Halothane is a halogenated hydrocarbon that is now seldom used in the First World. Isoflurane, sevoflurane and desflurane are halogenated ethers. The latter two agents are the most commonly used inhalational anaesthetic agents, although there are few PET studies involving desflurane.

The early work by Alkire, showing that isoflurane anaesthesia caused a 46% reduction in rCMRG with fairly uniform regional distribution, has already been mentioned (Alkire et al. 1997). Alkire then studied the effects of halothane on rCMRG, since this agent had been shown in earlier studies to cause less uniform rCMRG reductions (Alkire et al. 1999). Halothane anaesthesia was found to cause a 40% reduction in global rCMRG, but in keeping with the prior animal work, there were some regional differences, with the greater metabolic reductions being found in the basal forebrain, thalamus, limbic system, cerebellum and occipital cortex.

In the above studies, halothane and isoflurane were administered until an end point of loss of consciousness (the mean concentrations administered were 30% and 60% less than the concentrations required to prevent a response to a surgical incision—the so-called MAC value, a measure of potency). Kaisti studied the effects of surgical levels of sevoflurane anaesthesia—at concentrations that were 1.0, 1.5 and 2.0 multiples of the MAC value—on rCBF using $H_2{}^{15}O$ (Kaisti et al. 2002). At 1.0 MAC, sevoflurane caused global decreases in absolute rCBF (regional decreases were between 36% and 53% of baseline). Increasing doses caused a redistribution

of flow, with increases in rCBF in the thalamus and cerebellum, suggesting a disturbance of flow-metabolism coupling.

In a follow-up study, using $H_2{}^{15}O$, $^{15}O_2$ and C ^{15}O to study rCBF, $rCMRO_2$ and CBV, respectively, Kaisti titrated sevoflurane and propofol anaesthesia (with and without N_2O) to a moderate depth of anaesthesia, guided by the BIS (Kaisti et al. 2003). Sevoflurane concentrations were thus lower than in the previous study—0.75 × MAC without N_2O and 0.6 MAC with 70% N_2O. Sevoflurane without N_2O reduced the total CBF but only caused rCBF decreases in some areas (the occipital cortex, cerebellum, caudate and thalamus). The most significant changes in relative rCBF were in the thalamus, cuneus, frontoparietal cortex and cerebellum. Addition of N_2O caused a global return to baseline rCBF values, with the most significant relative rCBF increases in the occipital cortex and pons. With regard to $CMRO_2$, sevoflurane caused a global reduction, with absolute decreases in $rCMRO_2$ in all areas studied. The greatest reductions in relative $rCMRO_2$ were in the thalamus, cuneus, frontoparietal cortex and cerebellum. Addition of N_2O increased $rCMRO_2$ in the parieto-occipital region and cerebellum, but not quite to baseline/awake levels. At the doses studied, sevoflurane with and without N_2O did not alter rCBV. It was associated with a tendency towards reduced oxygen extraction fraction, more marked in the presence of N_2O, indicating that metabolism was more suppressed than flow, suggesting a degree of disturbed flow-metabolism coupling.

The above findings were generally confirmed by Schlunzen et al., although some increases in rCBF were found at lower doses (Schlunzen et al. 2004). The study involved use of $H_2{}^{15}O$ to study changes in rCBF associated with sub-anaesthetic to anaesthetic doses of sevoflurane (0.2, 0.35 and 1.0 MAC multiples). At all doses, sevoflurane increased rCBF in the anterior cingulate and decreased rCBF in the cerebellum. Compared with the baseline state, 0.2 MAC sevoflurane decreased rCBF in the inferior temporal cortex and lingual gyrus. 0.35 MAC increased rCBF in the middle temporal cortex and lingual gyrus while decreasing rCBF in the thalamus. The latter finding is unsurprising given that some volunteers displayed no response to a verbal stimulus, whereas other showed only sluggish responses. Finally, compared with 0.35 MAC, 1 MAC increased rCBF in the insula and decreased rCBF in the posterior cingulated, lingual gyrus, precuneus and frontal cortex. Similar patterns of changes were found in subsequent study, using similar methodology and equipotent isoflurane doses (Schlunzen et al. 2006).

When administering anaesthesia to patients with raised intracranial pressure who require surgical excision of space-occupying lesions, anaesthesiologists often employ a degree of hyperventilation in order to reduce CBF and intracranial pressure. Schlunzen thus studied the influence of hyperventilation on rCBF in volunteers subjected to surgical levels of sevoflurane anaesthesia (1 MAC) (Schlunzen et al. 2010). A reduction of the mean $PaCO_2$ from 5.5 to 3.8 kPa reduced the total CBF by 44%. The largest reductions in rCBF were found in the thalamus, medial occipitotemporal gyrus, cerebellum, precuneus, putamen and insula. This work clearly showed that under surgical levels of sevoflurane anaesthesia, CO_2 reactivity is maintained, with stronger responses in some areas than others.

Finally, this group also studied the effects of surgical levels of sevoflurane anaesthesia (1 MAC) on $rCMRO_2$ (Schlunzen et al. 2010). Total CMRG was reduced by 56%, and absolute rCMRG was decreased in all areas studied. The most significant relative rCMRG decreases were found in the lingual gyrus, occipital lobe and thalamus.

A few studies have addressed the molecular biology of the volatile agents. Among five subjects subjected to isoflurane anaesthesia, Alkire showed that the regional distribution of changes in rCBF correlated best with ex vivo-demonstrated muscarinic acetylcholine binding density, suggesting that the molecular action of isoflurane may involve antagonism of central acetylcholine pathways (Alkire and Haier 2001). On the other hand, Salmi showed that sevoflurane increased the distribution volume of ^{11}C-flumazenil in all areas studied (except pons and white matter), suggesting the involvement of $GABA_A$ receptors in the mechanism of action of sevoflurane (Salmi et al. 2004). This was concordant with a previous study of isoflurane, which showed a dose-dependent increase in distribution volume of ^{11}C-flumazenil (Gyulai et al. 2001).

Alkire and colleagues used PET to study the effects of sevoflurane at a higher system level (Alkire et al. 2008a). In the first step, they determined that exposure to low doses of sevoflurane—0.1% and 0.2% (0.05 and 0.1 MAC, respectively)—provided a subsequent mnemonic boost for emotional arousal but not neutral stimuli, presented during the sevoflurane exposure. This mnemonic boost was absent in volunteers administered with 0.25% sevoflurane. In the second step, ^{18}FDG PET was used to assess regional changes in glucose metabolism associated with 0.25% sevoflurane. Using structural equation modelling, they demonstrated that this dose blocked emotional memory by interfering with the amygdala to hippocampal connectivity.

44.13 PET and Nitrous Oxide

Nitrous oxide used to be commonly administered concomitantly with volatile anaesthetics. Although this practice is common, it is declining in frequency as environmental concerns have resulted in some departments no longer having inbuilt nitrous oxide supplies. On its own, the gas is a weak anaesthetic (administration of a partial pressure > 1 atm is required for general anaesthesia) but a reasonably strong analgesic, thanks to the fact that the drug acts as an antagonist at the NDMA receptor.

Few studies have used PET to study the neurophysiological changes associated with administration of nitrous oxide. Reinstrup used ^{133}Xe SPECT to study CBF changes associated with inhalation of 50% N_2O (Reinstrup et al. 1994). They found global increases in CBF, which were fairly uniform during normocapnia, although it remains possible that these changes were partly the result of Xe administration. It was also unclear whether these changes were the result of direct cerebral vasodilatation or from increases in metabolism. Later, the same group used ^{18}FDG to study

changes in glucose metabolism (Reinstrup et al. 2008). Inhalation of 50% nitrous oxide did not change global rCMRG, but did change the relative distribution of glucose metabolism, with 14% and 22% increases in the basal ganglia and thalamus, respectively.

In a study focused on sevoflurane and propofol, Kaisti and colleagues studied the effects of adjunct administration of 70% N_2O and found that N_2O counteracted some of the $rCMRO_2$ and rCBF reductions seen when propofol or sevoflurane was used alone (Kaisti et al. 2003). The findings all corroborated the findings of previous animal and human studies, in which other methods were used to study the cerebral blood flow and metabolic responses to N_2O.

44.14 PET and Xenon

Xenon is a rare (and expensive) noble gas and also a weak anaesthetic. Exposure to a 70% Xe will prevent purposeful movements in response to a surgical stimulus in 50% of volunteers (for comparison, the MAC of sevoflurane is 2.0%). The molecule is interesting because, like N_2O, it is also an NMDA antagonist, and it is probably for this reason that it may be neuroprotective.

PET studies of changes in rCBF have shown that in contrast to ketamine (also an NMDA antagonist), anaesthetic concentrations of Xe cause widespread decreases in rCBF, mostly marked in the cerebellum, thalamus and parietal cortex (Laitio et al. 2007). Findings for changes in rCMRG induced by Xe anaesthesia were also contrary to expectations, based on findings for N_2O and ketamine. Rex and colleagues found that Xe reduced total CMRG by 26% and decreased rCMRG in all areas studied (Rex et al. 2006). In a subsequent study, this group measured changes in rCBF associated with Xe anaesthesia, using $H_2{}^{15}O$ PET (Rex et al. 2008). Relative decreases in several cortical, subcortical and cerebellar areas were shown, with relative increases in white matter. These findings matched well with the previous pattern of findings with regard to rCBF, suggesting that flow-metabolism coupling is maintained with Xe.

Laitio and colleagues used ^{18}FDG and ^{15}O PET to study combined changes in rCMRG and rCBF associated with 67% Xe (Laitio et al. 2009). While the patterns of changes were broadly similar to those of Rex and colleagues, they found that the decreases in metabolism exceeded those of blood flow. When they calculated the rCBF/rCMRG ratio, they found that this was particularly increased in the insula, anterior and posterior cingulated and somatosensory cortex.

Although the patterns of changes in blood flow and metabolism are not too dissimilar to those found with the volatile anaesthetic agents, Xe does not influence ^{11}C-flumazenil binding, suggesting that the molecular mechanism of action of Xe does not involve an effect on the $GABA_A$ receptor (Salmi et al. 2008).

44.15 Summary and Conclusion

Early studies on the regional distribution of changes in cerebral metabolism associated with anaesthetic doses of isoflurane seemed to suggest uniform changes in keeping with a unitary hypothesis of a non-specific, physical molecular mechanism of action of the anaesthetic drugs. A limited number of studies have specifically studied the molecular mechanisms and site of action of the anaesthetic agents. In general, these studies have confirmed the findings of laboratory work using molecular biology techniques.

More recent PET studies have shown that the anaesthetic agents cause regionally specific effects on metabolism and flow and that these are probably the result of regionally specific distributions of neuronal $GABA_A$, NMDA and muscarinic ACh receptors. Most groups report global CBF and metabolic rate findings, absolute changes in rCBF and rCMRG or $rCMRO_2$ and then also changes in relative rCBF and rCMRG or $rCMRO_2$. The assumption inherent in the latter approach is that the greatest relative changes will happen in the regions where key anaesthetic effects are mediated. Different anaesthetic agents cause slightly different patterns of regional effects, but all cause an alteration in flow and/or metabolism in the thalamus. Anaesthetic-induced loss of consciousness appears to be associated with a significant reduction in blood flow and metabolism in the thalamus. While some investigators argue that this provides evidence that the thalamus is a key site of action of these agents (Alkire et al. 2000), caution is required, since these reductions in blood flow and metabolism may be the result of reduced cortical activity and thus reduced cortical input to the thalamus. EEG and electrocorticography studies suggest that the primary effect of anaesthetic agents is at the cortex, rather than at subcortical structures (Velly et al. 2007). EEG and fMRI studies provide contradictory evidence, with some suggesting that thalamocortical connectivity is maintained despite loss of consciousness (Boveroux et al. 2010; Boly et al. 2012), and others that preserved thalamocortical connectivity are a necessary prerequisite for consciousness (Barttfeld et al. 2015; Malekmohammadi et al. 2019).

Generally, the findings from PET studies of regional changes in blood flow and metabolism are in keeping with the known molecular sites of action. Xenon is one exception, since it has the same site of action as nitrous oxide and ketamine (NMDA receptor) yet has regional effects on blood flow and metabolism similar to those caused by the volatile anaesthetic agents (whose effects are mediated by action at $GABA_A$ and muscarinic Ach receptors and possibly also at K channels).

Much work remains to be done to understand how these molecular effects result in regional changes in activity and connectivity and changes in communication among distributed areas and how each of changes mediates alterations in consciousness.

References

Absalom AR, Green D (2013) NAP5: the tip of the iceberg, or all we need to know? Br J Anaesth 113(4):527–530

Adapa RM, Davis MH, Stamatakis EA, Absalom AR, Menon DK (2014) Neural correlates of successful semantic processing during propofol sedation. Hum Brain Mapp 35:2935–2949

Akeju O, Loggia ML, Catana C, Pavone KJ, Vazquez R, Rhee J et al (2014) Disruption of thalamic functional connectivity is a neural correlate of dexmedetomidine-induced unconsciousness. elife 4:e04499

Alkire MT (1998) Quantitative EEG correlations with brain glucose metabolic rate during anesthesia in volunteers. Anesthesiology 89(2):323–333

Alkire MT, Haier RJ (2001) Correlating in vivo anaesthetic effects with ex vivo receptor density data supports a GABAergic mechanism of action for propofol, but not for isoflurane. Br J Anaesth 86(5):618–626

Alkire MT, Miller J (2005) General anesthesia and the neural correlates of consciousness. Prog Brain Res 150:229–244

Alkire MT, Haier RJ, Barker SJ, Shah NK, Wu JC, Kao YJ (1995) Cerebral metabolism during propofol anesthesia in humans studied with positron emission tomography. Anesthesiology 82(2):393–403

Alkire MT, Haier RJ, Shah NK, Anderson CT (1997) Positron emission tomography study of regional cerebral metabolism in humans during isoflurane anesthesia. Anesthesiology 86(3):549–557

Alkire MT, Pomfrett CJ, Haier RJ, Gianzero MV, Chan CM, Jacobsen BP, Fallon JH (1999) Functional brain imaging during anesthesia in humans: effects of halothane on global and regional cerebral glucose metabolism. Anesthesiology 90(3):701–709

Alkire MT, Haier RJ, Fallon JH (2000) Toward a unified theory of narcosis: brain imaging evidence for a thalamocortical switch as the neurophysiologic basis of anesthetic-induced unconsciousness. Conscious Cogn 9(3):370–386

Alkire MT, Gruver R, Miller J, McReynolds JR, Hahn EL, Cahill L (2008a) Neuroimaging analysis of an anesthetic gas that blocks human emotional memory. Proc Natl Acad Sci U S A 105(5):1722–1727

Alkire MT, Hudetz AG, Tononi G (2008b) Consciousness and anesthesia. Science 322(5903):876–880

Angel A (1993) Central neuronal pathways and the process of anaesthesia. Br J Anaesth 71(1):148–163

Arhem P, Klement G, Nilsson J (2003) Mechanisms of anesthesia: towards integrating network, cellular, and molecular level modeling. Neuropsychopharmacology 28(Suppl 1):S40–S47

Barttfeld P, Bekinschtein TA, Salles A, Stamatakis EA, Adapa R, Menon DK, Sigman M (2015) Factoring the brain signatures of anesthesia concentration and level of arousal across individuals. NeuroImage Clin 9:385–391

Belelli D, Lambert JJ, Peters JA, Wafford K, Whiting PJ (1997) The interaction of the general anesthetic etomidate with the gamma-aminobutyric acid type A receptor is influenced by a single amino acid. Proc Natl Acad Sci U S A 94(20):11031–11036

Bishu S, Schmidt KC, Burlin TV, Channing MA, Horowitz L, Huang T, Liu ZH, Qin M, Vuong BK, Unterman AJ, Xia Z, Zametkin A, Herscovitch P, Quezado Z, Smith CB (2009) Propofol anesthesia does not alter regional rates of cerebral protein synthesis measured with L-[1-(11) C]leucine and PET in healthy male subjects. J Cereb Blood Flow Metab 29(5):1035–1047

Boly M, Moran R, Murphy M, Boveroux P, Bruno MA, Noirhomme Q, Ledoux D, Bonhomme V, Brichant JF, Tononi G, Laureys S, Friston K (2012) Connectivity changes underlying spectral EEG changes during propofol-induced loss of consciousness. J Neurosci 32(20):7082–7090

Bonhomme V, Fiset P, Meuret P, Backman S, Plourde G, Paus T, Bushnell MC, Evans AC (2001) Propofol anesthesia and cerebral blood flow changes elicited by vibrotactile stimulation: a positron emission tomography study. J Neurophysiol 85(3):1299–1308

Bonhomme V, Maquet P, Phillips C, Plenevaux A, Hans P, Luxen A, Lamy M, Laureys S (2008) The effect of clonidine infusion on distribution of regional cerebral blood flow in volunteers. Anesth Analg 106(3):899–909, table of contents

Boveroux P, Vanhaudenhuyse A, Bruno MA, Noirhomme Q, Lauwick S, Luxen A, Degueldre C, Plenevaux A, Schnakers C, Phillips C, Brichant JF, Bonhomme V, Maquet P, Greicius MD, Laureys S, Boly M (2010) Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. Anesthesiology 113(5):1038–1053

Braestrup C, Albrechtsen R, Squires RF (1977) High densities of benzodiazepine receptors in human cortical areas. Nature 269(5630):702–704

Brown EN, Lydic R, Schiff ND (2010) General anesthesia, sleep, and coma. N Engl J Med 363(27):2638–2650, no. 1533-4406; 0028-4793

Cavazzuti M, Porro CA, Barbieri A, Galetti A (1991) Brain and spinal cord metabolic activity during propofol anaesthesia. Br J Anaesth 66(4):490–495

Dam M, Ori C, Pizzolato G, Ricchieri GL, Pellegrini A, Giron GP, Battistin L (1990) The effects of propofol anesthesia on local cerebral glucose utilization in the rat. Anesthesiology 73(3):499–505

Davidson AJ, Disma N, de Graaff JC et al (2016) Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet 387(10015):239–250

Davis MH, Coleman MR, Absalom AR, Rodd JM, Johnsrude IS, Matta BF, Owen AM, Menon DK (2007) Dissociating speech perception and comprehension at reduced levels of awareness. Proc Natl Acad Sci U S A 104(41):16032–16037

Enna SJ, Snyder SH (1977) GABA receptor binding in frog spinal cord and brain. J Neurochem 28(4):857–860

Fiset P, Paus T, Daloze T, Plourde G, Meuret P, Bonhomme V, Hajj-Ali N, Backman SB, Evans AC (1999) Brain mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomographic study. J Neurosci 19(13):5506–5513

Franks NP (2008) General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. Nat Rev Neurosci 9(5):370–386

Franks NP, Lieb WR (1984) Do general anaesthetics act by competitive binding to specific receptors? Nature 310(5978):599–601, no. 0028-0836; 0028-0836

Franks NP, Lieb WR (1993) Selective actions of volatile general anaesthetics at molecular and cellular levels. Br J Anaesth 71(1):65–76

Franks NP, Lieb WR (1997) Inhibitory synapses. Anaesthetics set their sites on ion channels. Nature 389(6649):334–335

Franks NP, Lieb WR (2004) Seeing the light: protein theories of general anesthesia. 1984. Anesthesiology 101(1):235–237

Gyulai FE, Mintun MA, Firestone LL (2001) Dose-dependent enhancement of in vivo GABA(A)-benzodiazepine receptor binding by isoflurane. Anesthesiology 95(3):585–593, no. 0003-3022; 0003-3022

Hales TG, Lambert JJ (1991) The actions of propofol on inhibitory amino acid receptors of bovine adrenomedullary chromaffin cells and rodent central neurones. Br J Pharmacol 104(3):619–628

Hameroff SR (2006) The entwined mysteries of anesthesia and consciousness: is there a common underlying mechanism? Anesthesiology 105(2):400–412

Haydon DA, Urban BW (1983) The effects of some inhalation anaesthetics on the sodium current of the squid giant axon. J Physiol 341:429–439

Haydon DA, Urban BW (1986) The actions of some general anaesthetics on the potassium current of the squid giant axon. J Physiol 373:311–327

Holmes SE, Gallezot JD, Davis MT et al (2019) Measuring the effects of ketamine on mGluR5 using [(18)F]FPEB and PET. J Cereb Blood Flow Metab. https://doi.org/10.1177/271678X19886316

Imas OA, Ropella KM, Wood JD, Hudetz AG (2006) Isoflurane disrupts anterio-posterior phase synchronization of flash-induced field potentials in the rat. Neurosci Lett 402(3):216–221

Jevtovic-Todorovic V, Absalom AR, Blomgren K, Brambrink A, Crosby G, Culley DJ et al (2013) Anaesthetic neurotoxicity and neuroplasticity: an expert group report and statement based on the BJA Salzburg Seminar. Br J Anaesth 111(2):143–151

Kaisti KK, Metsahonkala L, Teras M, Oikonen V, Aalto S, Jaaskelainen S, Hinkka S, Scheinin H (2002) Effects of surgical levels of propofol and sevoflurane anesthesia on cerebral blood flow in healthy subjects studied with positron emission tomography. Anesthesiology 96(6):1358–1370

Kaisti KK, Langsjo JW, Aalto S, Oikonen V, Sipila H, Teras M, Hinkka S, Metsahonkala L, Scheinin H (2003) Effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption, and blood volume in humans. Anesthesiology 99(3):603–613

Kissin I (1993) General anesthetic action: an obsolete notion? Anesth Analg 76(2):215–218

Kulli J, Koch C (1991) Does anesthesia cause loss of consciousness? Trends Neurosci 14(1):6–10

Laaksonen L, Kallioinen M, Långsjö J et al (2018) Comparative effects of dexmedetomidine, propofol, sevoflurane, and S-ketamine on regional cerebral glucose metabolism in humans: a positron emission tomography study. Br J Anaesth 121(1):281–290

Laitio RM, Kaisti KK, Långsjö JW, Aalto S, Salmi E, Maksimow A, Aantaa R, Oikonen V, Sipila H, Parkkola R, Scheinin H (2007) Effects of xenon anesthesia on cerebral blood flow in humans: a positron emission tomography study. Anesthesiology 106(6):1128–1133

Laitio RM, Långsjö JW, Aalto S, Kaisti KK, Salmi E, Maksimow A, Aantaa R, Oikonen V, Viljanen T, Parkkola R, Scheinin H (2009) The effects of xenon anesthesia on the relationship between cerebral glucose metabolism and blood flow in healthy subjects: a positron emission tomography study. Anesth Analg 108(2):593–600

Långsjö JW, Kaisti KK, Aalto S, Hinkka S, Aantaa R, Oikonen V, Sipila H, Kurki T, Silvanto M, Scheinin H (2003) Effects of subanesthetic doses of ketamine on regional cerebral blood flow, oxygen consumption, and blood volume in humans. Anesthesiology 99(3):614–623

Långsjö JW, Salmi E, Kaisti KK, Aalto S, Hinkka S, Aantaa R, Oikonen V, Viljanen T, Kurki T, Silvanto M, Scheinin H (2004) Effects of subanesthetic ketamine on regional cerebral glucose metabolism in humans. Anesthesiology 100(5):1065–1071

Långsjö JW, Maksimow A, Salmi E, Kaisti K, Aalto S, Oikonen V, Hinkka S, Aantaa R, Sipila H, Viljanen T, Parkkola R, Scheinin H (2005) S-ketamine anesthesia increases cerebral blood flow in excess of the metabolic needs in humans. Anesthesiology 103(2):258–268

Långsjö JW, Alkire MT, Kaskinoro K, Hayama H, Maksimow A, Kaisti KK, Aalto S, Aantaa R, Jääskeläinen SK, Revonsuo A, Scheinin H (2012) Returning from oblivion: imaging the neural core of consciousness. J Neurosci 32(14):4935–4943

Lee U, Kim S, Noh GJ, Choi BM, Hwang E, Mashour GA (2009) The directionality and functional organization of frontoparietal connectivity during consciousness and anesthesia in humans. Conscious Cogn 18(4):1069–1078

Lindholm ML, Traff S, Granath F, Greenwald SD, Ekbom A, Lennmarken C, Sandin RH (2009) Mortality within 2 years after surgery in relation to low intraoperative bispectral index values and preexisting malignant disease. Anesth Analg 108(2):508–512, no. 1526-7598

Lydic R, Baghdoyan HA (2005) Sleep, anesthesiology, and the neurobiology of arousal state control. Anesthesiology 103(6):1268–1295

Malekmohammadi M, Price CM, Hudson AE, DiCesare JAT, Pouratian N (2019) Propofol-induced loss of consciousness is associated with a decrease in thalamocortical connectivity in humans. Brain 142(8):2288–2302

Mandal PK, Fodale V (2009) Isoflurane and desflurane at clinically relevant concentrations induce amyloid beta-peptide oligomerization: an NMR study. Biochem Biophys Res Commun 379(3):716–720

Mashour GA (2006) Integrating the science of consciousness and anesthesia. Anesth Analg 103(4):975–982

Mashour GA, Kent C, Picton P, Ramachandran SK, Tremper KK, Turner CR, Shanks A, Avidan MS (2013) Assessment of intraoperative awareness with explicit recall: a comparison of 2 methods. Anesth Analg 116:889–891

Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, Macrae CN (2007) Wandering minds: the default network and stimulus-independent thought. Science (New York, NY) 315(5810):393–395

Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G (2005) Breakdown of cortical effective connectivity during sleep. Science 309(5744):2228–2232

Massimini M, Ferrarelli F, Esser SK, Riedner BA, Huber R, Murphy M, Peterson MJ, Tononi G (2007) Triggering sleep slow waves by transcranial magnetic stimulation. Proc Natl Acad Sci U S A 104(20):8496–8501

McCann ME, de Graaff JC, Dorris L et al (2019) Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an international, multicentre, randomised, controlled equivalence trial. Lancet 393(10172):664–677

Mihic SJ, Ye Q, Wick MJ, Koltchine VV, Krasowski MD, Finn SE, Mascia MP, Valenzuela CF, Hanson KK, Greenblatt EP, Harris RA, Harrison NL (1997) Sites of alcohol and volatile anaesthetic action on GABA(A) and glycine receptors. Nature 389(6649):385–389

Monk TG, Saini V, Weldon BC, Sigl JC (2005) Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg 100(1):4–10, no. 0003-2999; 0003-2999

Naci L, Haugg A, MacDonald A, Anello M, Houldin E, Naqshbandi G-LL, Arango M, Harle C, Cusack R, Owen A (2018) Functional diversity of brain networks supports consciousness and verbal intelligence. Sci Rep 8:13259

Noirhomme Q, Boly M, Bonhomme V, Boveroux P, Phillips C, Peigneux P, Soddu A, Luxen A, Moonen G, Maquet P, Laureys S (2009) Bispectral index correlates with regional cerebral blood flow during sleep in distinct cortical and subcortical structures in humans. Arch Ital Biol 147(1–2):51–57

Ori C, Dam M, Pizzolato G, Battistin L, Giron G (1986) Effects of isoflurane anesthesia on local cerebral glucose utilization in the rat. Anesthesiology 65(2):152–156

Pandit JJ, Andrade J, Bogod DG, Hitchman JM et al (2014) 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors. Br J Anaesth 113(4):549–559

Prielipp RC, Wall MH, Tobin JR, Groban L, Cannon MA, Fahey FH, Gage HD, Stump DA, James RL, Bennett J, Butterworth J (2002) Dexmedetomidine-induced sedation in volunteers decreases regional and global cerebral blood flow. Anesth Analg 95(4):1052–1059, table of contents

Prys-Roberts C (1987) Anaesthesia: a practical or impractical construct? Br J Anaesth 59:1341–1345

Reinstrup P, Ryding E, Algotsson L, Berntman L, Uski T (1994) Effects of nitrous oxide on human regional cerebral blood flow and isolated pial arteries. Anesthesiology 81(2):396–402

Reinstrup P, Ryding E, Ohlsson T, Sandell A, Erlandsson K, Ljunggren K, Salford LG, Strand S, Uski T (2008) Regional cerebral metabolic rate (positron emission tomography) during inhalation of nitrous oxide 50% in humans. Br J Anaesth 100(1):66–71

Rex S, Schaefer W, Meyer PH, Rossaint R, Boy C, Setani K, Bull U, Baumert JH (2006) Positron emission tomography study of regional cerebral metabolism during general anesthesia with xenon in humans. Anesthesiology 105(5):936–943

Rex S, Meyer PT, Baumert JH, Rossaint R, Fries M, Bull U, Schaefer WM (2008) Positron emission tomography study of regional cerebral blood flow and flow-metabolism coupling during general anaesthesia with xenon in humans. Br J Anaesth 100(5):667–675

Reynolds DS, Rosahl TW, Cirone J, O'Meara GF, Haythornthwaite A, Newman RJ, Myers J, Sur C, Howell O, Rutter AR, Atack J, Macaulay AJ, Hadingham KL, Hutson PH, Belelli D, Lambert JJ, Dawson GR, McKernan R, Whiting PJ, Wafford KA (2003) Sedation and anesthesia mediated by distinct GABA(A) receptor isoforms. J Neurosci 23(24):8608–8617

Rudolph U, Antkowiak B (2004) Molecular and neuronal substrates for general anaesthetics. Nat Rev Neurosci 5(9):709–720

Salmi E, Kaisti KK, Metsahonkala L, Oikonen V, Aalto S, Nagren K, Hinkka S, Hietala J, Korpi ER, Scheinin H (2004) Sevoflurane and propofol increase 11C-flumazenil binding to gamma-aminobutyric acid A receptors in humans. Anesth Analg 99(5):1420–1426

Salmi E, Langsjo JW, Aalto S, Nagren K, Metsahonkala L, Kaisti KK, Korpi ER, Hietala J, Scheinin H (2005) Subanesthetic ketamine does not affect 11C-flumazenil binding in humans. Anesth Analg 101(3):722–725

Salmi E, Laitio RM, Aalto S, Maksimow AT, Langsjo JW, Kaisti KK, Aantaa R, Oikonen V, Metsahonkala L, Nagren K, Korpi ER, Scheinin H (2008) Xenon does not affect gamma-aminobutyric acid type A receptor binding in humans. Anesth Analg 106(1):129–134

Sandin RH, Enlund G, Samuelsson P, Lennmarken C (2000) Awareness during anaesthesia: a prospective case study. Lancet 355(9205):707–711

Schlunzen L, Vafaee MS, Cold GE, Rasmussen M, Nielsen JF, Gjedde A (2004) Effects of subanaesthetic and anaesthetic doses of sevoflurane on regional cerebral blood flow in healthy volunteers. A positron emission tomographic study. Acta Anaesthesiol Scand 48(10):1268–1276

Schlunzen L, Cold GE, Rasmussen M, Vafaee MS (2006) Effects of dose-dependent levels of isoflurane on cerebral blood flow in healthy subjects studied using positron emission tomography. Acta Anaesthesiol Scand 50(3):306–312

Schlunzen L, Vafaee MS, Juul N, Cold GE (2010) Regional cerebral blood flow responses to hyperventilation during sevoflurane anaesthesia studied with PET. Acta Anaesthesiol Scand 54(5):610–615

Schlunzen L, Juul N, Hansen KV, Cold GE (2012) Regional cerebral blood flow and glucose metabolism during propofol anaesthesia in healthy subjects studied with positron emission tomography. Acta Anaesthesiol Scand 56(2):248–255

Sebel PS, Bowdle TA, Ghoneim MM, Rampil IJ, Padilla RE, Gan TJ, Domino KB (2004) The incidence of awareness during anesthesia: a multicenter United States study. Anesth Analg 99(3):833–839

Short TG, Campbell D, Frampton C et al (2019) Anaesthetic depth and complications after major surgery: an international, randomised controlled trial. Lancet 394(10212):1907–1914

Spies M, James GM, Berroterán-Infante N, Ibeschitz H, Kranz GS, Unterholzner J, Godbersen M, Gryglewski G, Hienert M, Jungwirth J et al (2018) Assessment of ketamine binding of the serotonin transporter in humans with positron emission tomography. Int J Neuropsychopharmacol 21:145–153

Stamatakis EA, Adapa RM, Absalom AR, Menon DK (2010) Changes in resting neural connectivity during propofol sedation. PLoS One 5(12):e14224, no. 1932-6203; 1932-6203

Varley TF, Luppi A, Pappas I, Naci L, Adapa R, Owen A, Menon DK, Stamatakis EA (2019) Consciousness and brain functional complexity in propofol anaesthesia. bioRxiv: 680447

Velly LJ, Rey MF, Bruder NJ, Gouvitsos FA, Witjas T, Regis JM, Peragut JC, Gouin FM (2007) Differential dynamic of action on cortical and subcortical structures of anesthetic agents during induction of anesthesia. Anesthesiology 107(2):202–212

Vollenweider FX, Leenders KL, Oye I, Hell D, Angst J (1997) Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). Eur Neuropsychopharmacol 7(1):25–38

Walker EM, Bell M, Cook TM, Grocott MP, Moonesinghe SR (2016) SNAP-1 investigator group. Patient reported outcome of adult perioperative anaesthesia in the United Kingdom: a cross-sectional observational study. Br J Anaesth 117:758–766

Whittington RA, Virag L, Marcouiller F et al (2011) Propofol directly increases tau phosphorylation. PLoS One 6(1):e16648

Xie G, Gunn RN, Dagher A, Daloze T, Plourde G, Backman SB, Diksic M, Fiset P (2004) PET quantification of muscarinic cholinergic receptors with [N-11C-methyl]-benztropine and application to studies of propofol-induced unconsciousness in healthy human volunteers. Synapse 51(2):91–101

Xie G, Deschamps A, Backman SB, Fiset P, Chartrand D, Dagher A, Plourde G (2011) Critical involvement of the thalamus and precuneus during restoration of consciousness with physostigmine in humans during propofol anaesthesia: a positron emission tomography study. Br J Anaesth 106(4):548–557

Zezula J, Cortes R, Probst A, Palacios JM (1988) Benzodiazepine receptor sites in the human brain: autoradiographic mapping. Neuroscience 25(3):771–795