Anesthetics and cerebral metabolism
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Purpose of review
This review focuses on the utilization of the effects of general anesthetics on cerebral metabolism as revealed by imaging for therapeutic and preventive purposes, for understanding mechanisms of anesthetic action, and for elucidating mechanisms of cerebral processing in humans.

Recent findings
General anesthetics suppress cerebral metabolism significantly. This effect has been used for neuroprotection during inadequate cerebral blood flow. With the advent of noninvasive imaging techniques, this suppression has also been used to image and map the sites of anesthetic action in the living human brain. Volatile agents, intravenous anesthetics, and analgesics have all begun to be explored using mostly positron emission tomography. The ability of anesthetics to change global baseline brain metabolism has created the opportunity to examine the relevance of global baseline (resting) brain activity in terms of region-specific cerebral processing.

Summary
Anesthetics experimentally appear to be useful for neuroprotection, at least during the early post-ischemic period. Identification of the cerebral sites of anesthetic action by in vivo human brain imaging provides new insights into the mechanism of action of these agents. Anesthetic-related manipulation of baseline brain metabolism demonstrates the significant contribution of this global activity to regional cerebral processing.

Keywords
anesthetics, cerebral metabolism, positron emission tomography, functional magnetic resonance imaging

Introduction
The effect of general anesthetics on cerebral metabolism is relevant for a number of reasons. Since anesthetics suppress brain metabolism, excitatory transmission, and enhance inhibition, they have been considered in the past four decades as natural candidates to produce brain protection under ischemic circumstances [1]. Due to the fact that the sites of general anesthetic action remain largely unknown, general anesthetics’ effect on cerebral metabolism also offers a unique opportunity to investigate potential sites of action in the brain using noninvasive imaging techniques. In the past 15 years, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have become available to map brain metabolism or activity in vivo in the absence and presence of pharmacological perturbations, thus allowing the identification of brain areas that are affected by these agents [2]. In addition to brain protection and elucidation of sites of drug action, the effect of anesthetics on cerebral metabolism has made it feasible to address more fundamental aspects of brain function as well. Specifically, the ability of anesthetics to alter brain metabolism has been exploited as a tool to examine the contribution of global baseline or resting cerebral activity to specific tasks controlled by discrete brain areas [3**].

Anesthetics and neuroprotection
Ischemic brain injury, which is a potentially devastating complication of anesthesia and surgery, is the result of inadequate cerebral blood flow and has consequently triggered a significant search for pharmacological strategies of prevention and treatment. Among the logical candidates are general anesthetics that are known to suppress cerebral metabolism by enhancing γ-amino butyric acidergic-A inhibitory mechanisms and inhibiting excitatory processes [4]. This expectation has been partly confirmed in animal models of focal [5], hemispheric [6], and global [7] ischemia, some of which show significant neuroprotective effects of these agents.

An important caveat of these studies, however, is the fact that the studied period following the ischemic episode was on the scale of days, which is in contrast to the observation that affected cells remain vulnerable for at least a couple of weeks into the post-ischemic period [8]. In order to address this, recent studies have begun to expand the time scale of their investigations to 2 weeks to 3 months after injury. Kawaguchi et al. [9] showed that
isoﬂurane was associated with signiﬁcant neuroprotection, which diminished after 2 weeks. Similarly, Elsersy et al. [10••] demonstrated that initial isoﬂurane-evoked neuroprotective effects observed 5 days into the post-ischemic period disappeared by 3 weeks and remained indiscernible 3 months after the ischemic injury. These observations have been extended to propofol also [11•].

These studies clearly indicate the potential of general anesthetics in the prevention and treatment of ischemic brain injury, and at the same time they also identify components of the ﬁnal injury that manifest later in the post-ischemic period. These components are most likely mediated by mechanisms unrelated to neuronal activity as suggested by the lack of impact of general anesthetics’ suppressant effect on cerebral metabolism. For example, programmed cell death, or apoptosis, has been proposed as one of the putative mechanisms underlying delayed neuronal injury [12] and it may not be sensitive to anesthetic suppression. There is, therefore, a necessity for multi-prong approaches to comprehensive and effective neuroprotection.

In vivo mapping of sites of anesthetic action by imaging anesthetic affects on cerebral metabolism

Although anesthetics have been in extensive use for decades, the brain areas participating in their mechanisms of action remain obscure. Abundant in vitro and in vivo animal experiments yielded a number of putative sites and targets [4]. In addition to the obvious limitation of animal studies in terms of their extension to humans, however, the relevance of these ﬁndings have remained questionable mostly because of the application of destructive techniques in these approaches sacriﬁcing the integrity of the studied biological systems.

Recent advances in in vivo imaging techniques, such as PET and fMRI have made it feasible to elucidate sites of drug action in the living human by mapping their effect on either regional cerebral metabolic rate (rCMR) with PET, or regional cerebral blood ﬂow (rCBF) with PET and fMRI as an index of neuronal activity [2]. The link between rCMR and neuroenergetics as a reﬂection of actual neuronal activity was provided by 13C magnetic resonance spectroscopy experiments both in rats and humans [13,14]. These studies established a stoichiometric relationship between glucose metabolism and neurotransmission energetics by measuring glucose and neurotransmitter concentrations in vivo over time. The tight coupling between rCMR and rCBF was ﬁrst suggested by Roy and Sherrington [15], and conﬁrmed by independent autoradiographic measurement of the two parameters [16,17]. The methodological aspects of these powerful imaging techniques are reviewed elsewhere in detail [2].

Imaging anesthetic action by positron emission tomography

Recent human PET studies mapping regional glucose metabolism changes in the presence of isoﬂurane [18], halothane [19], and propofol [20] titrated to the point of unconsciousness revealed global cerebral metabolic decreases in the range of 40–55% (Fig. 1). This change showed a positive correlation with relevant electroencephalography parameters strengthening the functional relevance of the imaging studies [21].

In addition to the global changes in metabolism, halothane and propofol were associated with regional alterations as well. Halothane administration resulted in region-speciﬁc decreases in the thalamus, basal forebrain, occipital area, and the limbic cortex [19]. Propofol-related regional decreases occurred in the temporal and occipital cortices [20].

Using the data set of these human studies, the same group attempted to ﬁnd brain regions that were commonly affected by isoﬂurane and halothane in an attempt to identify the sites that ultimately underlie the mechanism of inhalational anesthetic-related unconsciousness [22]. The conjunction analysis of the isoﬂurane and halothane dataset revealed decreases in the thalamus, midbrain reticular formation, basal forebrain, and occipital cortex.

Propofol was also studied with rCBF PET imaging in human volunteers showing global dose-related blood ﬂow as well as regional decreases in the thalamus, basal forebrain, posterior cingulate, and occipital cortices [23]. Correlation analysis also revealed synchronous changes in the thalamus and midbrain indicating an intimate functional relationship between these structures. In a second study, the same group conﬁrmed and extended these observations to thalamic and somatosensory cortical responses to vibrotactile stimulation [24]. They showed a dose-dependent decrease in vibrotactile responses in the somatosensory cortex at sedative concentrations of propofol, whereas the thalamic response was affected only at anesthetic levels.

Benzodiazepines were also studied with rCBF PET in humans. Sedative levels of midazolam were associated with rCBF decreases in the thalamus, anterior cingulate, prefrontal, parietal, and temporal cortices [25–27]. The involvement of the thalamus in benzodiazepine-related sedation was conﬁrmed by other human PET studies as well [28,29].

Although some of the brain areas identiﬁed as putative targets of anesthesia seem to be inconsistent across the various studies, a few regions emerge as common mediators of hypnosis. For example, the consistent
deactivation of the thalamus in the presence of anesthetics and benzodiazepines together with midbrain areas, as well as prefrontal and occipital cortical regions suggest that these structures represent mechanistic components of a hypnotic cerebral network.

**Imaging analgesic action by positron emission tomography**

Better understanding of the interaction between systemic analgesics and cerebral nociceptive mechanisms could facilitate the development of more efficient pain treatment strategies. The complexity of the human pain experience suggests that analgesics, such as opioids and nitrous oxide, in analgesic concentrations, exert at least part of their effects via supraspinal neural networks [30,31]. Due to the previous lack of sensitive noninvasive techniques, this potentially important interaction had not been explored in humans until recently.

With the advent of rCBF PET, human studies have found that noxious peripheral thermal stimuli evoke highly localized cerebral rCBF increases in the thalamus, anterior cingulate, prefrontal cortex, insula, inferior parietal cortex, supplementary motor area, and with less consistency, the primary and secondary somatosensory cortices [32]. The anterior cingulate is thought to process the affective motivational, whereas, the somatosensory cortices and insula are considered to be responsible for the somatosensory, the prefrontal and parietal cortices for the memory, and the supplementary motor area for the motor elements of pain sensation.

Opioid analgesics seem to affect this very same network. Human PET studies showed rCBF increases in response to remifentanil in the prefrontal, inferior parietal cortices, and supplementary motor area at low concentrations. Higher doses were associated with the additional recruitment of the anterior cingulate [33]. Previous human studies with fentanyl are in partial agreement with these observations. Bolus injections of fentanyl alone resulted in rCBF increases in the anterior cingulated, prefrontal cortex, motor cortex, and caudate nuclei in addition to decreases in the thalamus and posterior cingulated cortex [34]. When fentanyl was administered in the presence of peripheral pain stimulation, surprisingly, enhancement of pain-induced rCBF increases were found in the supplementary motor area and prefrontal cortex suggesting that these areas are the neuroanatomical substrates of fentanyl analgesia in the human brain [35].

In a similar PET study [36], nitrous oxide, a frequently used component of general anesthetics at higher concentrations, administered at the analgesic 20% level, was associated with significant rCBF increases in the anterior cingulate and prefrontal cortices [36]. When it was administered in the presence of peripheral noxious stimulation, the pain-related responses in the thalamus, anterior cingulate, and supplementary motor area (Fig. 2) were abolished, and new areas of activation occurred in the infralimbic and orbitofrontal cortices (Fig. 3) indicating involvement of these areas in nitrous oxide’s analgesic mechanisms of action [37].

**Exploiting anesthetics’ effect on brain metabolism: toward a deeper understanding of cerebral processing**

The suppressing effect of anesthetics on cerebral metabolism offers a unique opportunity to examine the contribution of global, or background cerebral activity to specific tasks carried out by discrete brain areas. In these approaches, the magnitude of a specific task-related activation is measured in the relevant brain area at high and low global brain metabolism levels, or in the presence of light versus deep anesthesia, respectively, to assess the contribution of this background activity to task-related responses. The assumption is that if the magnitude of
activation is the same in both conditions, then, task-related cerebral processing does not require the participation of baseline processes, whereas, if the magnitude of activation is greater in the anesthetized condition, the contribution of baseline activity is significant requiring the regeneration of activity to awake levels.

Figure 2. Statistical parametric maps of neuronal activation during pain stimulation alone

Pixels that are significant at the given threshold of $P < 0.01$ are displayed on single sagittal, coronal, and transverse projections of the brain as lighter shades of gray, where the lightest shade indicates the greatest degree of activation. Gyalai et al. [37] provide methodological details and anatomic locations. R, right hemisphere; L, left hemisphere; VAC, vertical line through the anterior commissure; VPC, vertical line through the posterior commissure. Adapted with permission [37].

Figure 3. Statistical parametric maps of neuronal activation during pain stimulation in the presence of nitrous oxide

The activation pattern reflects nitrous oxide-modulated pain responses because only activations associated with nitrous oxide alone are subtracted from the image obtained during the combined administration of pain and nitrous oxide. Pixels that are significant at the given threshold of $P < 0.01$ are displayed on single sagittal, coronal, and transverse projections of the brain as lighter shades of gray, where the lightest shade indicates the greatest degree of activation. Gyalai et al. [37] provide methodological details and anatomic locations. R, right hemisphere; L, left hemisphere; VAC, vertical line through the anterior commissure; VPC, vertical line through the posterior commissure. Adapted with permission [37].
Toward this goal, first, the relationship between brain metabolism and neuronal firing activity was established. Brain metabolism was measured with an fMRI methodology, reviewed in detail elsewhere [2], in the presence of forepaw stimulation in rats, and the obtained values were correlated with neuronal firing activity in the somatosensory cortex [38]. This was necessary to establish a clear relationship between brain metabolism and neuronal activity. The comparison of metabolism and firing rate increases in the presence of light versus deep anesthesia revealed that the absolute level of activity during stimulation is the same in the two conditions, which means that the magnitude of increase is significantly greater during deep anesthesia than during light anesthesia (Fig. 4) [38]. This indicates that cerebral processing requires a certain level of activity as opposed to a certain amount of increase in activity.

In a broader sense, this observation has a significant impact on our thinking about cerebral processing. As opposed to the more traditional view that cerebral processing takes place in a highly localized fashion in discrete brain areas, the observed contribution of global baseline activity to local cortical processing suggests the existence of a more global workspace, in which certain aspects of processing are localized, but others are carried out in a topographically non-specific manner involving highly distributed neural networks [3**].

Conclusion

The relevance of general anesthetics’ effect on cerebral metabolism is at least three-fold. The suppressant effect of these agents on brain metabolism is exploited for neuroprotection under ischemic circumstances. Using state-of-the-art noninvasive imaging techniques, this same effect is mapped with remarkable precision to identify the sites of anesthetic action in the living human brain. Lastly, manipulation of brain metabolism and activity using anesthetics has the potential to shed light on fundamental mechanisms of cerebral processing.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
** of outstanding interest


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