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Critical involvement of the thalamus and precuneus during restoration of consciousness with physostigmine in humans during propofol anaesthesia: a positron emission tomography study

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Editor's key points

- Functional brain imaging shows that anaesthetic-induced unconsciousness is associated with decreased thalamic and cortical activity.
- Unconsciousness and functional brain imaging changes may, however, be unrelated effects of general anaesthetics.
- Physostigmine can restore consciousness during propofol anaesthesia even if the concentration of propofol is unchanged.
- This strategy demonstrated a functional link between unconsciousness and decreased activity in thalamus and precuneus.

Background. Functional brain imaging offers a way to investigate how general anaesthetics impair consciousness. However, functional imaging changes may result from drug effects unrelated to hypnosis. Establishing a causal link with loss of consciousness is thus difficult.

Methods. To identify changes of neuronal activity functionally linked to the level of consciousness, physostigmine was used to restore consciousness without changing the anaesthetic concentration in 11 subjects anaesthetized with propofol. Eight subjects (responders) regained consciousness after physostigmine and three did not (non-responders). Positron emission tomography was used to measure regional cerebral blood flow (rCBF); during baseline (awake), after anaesthesia-induced loss of consciousness, after physostigmine administration, and recovery. In addition to subtraction analyses, we used conjunction analysis in the responders to identify changes common to the baseline–anaesthesia and physostigmine–anaesthesia contrasts.

Results. Complete data were available for seven subjects (four responders and three non-responders). The analyses revealed that unconsciousness was associated with rCBF decreases in the thalamus and precuneus. Restoration of consciousness by physostigmine was associated with rCBF increases in these same structures, with the strongest effect in the thalamus.

Conclusions. The results provide strong evidence that reductions in rCBF in the thalamus and precuneus are functionally related to propofol-induced unconsciousness independently of any non-specific effects of propofol. These observations confirm that the thalamus and precuneus are key elements to understand how general anaesthetics cause unconsciousness and how patients wake up from anaesthesia. Furthermore, they are consistent with the notion that anaesthetic-induced unconsciousness is associated with reduced cholinergic activation.

Keywords: brain imaging; cerebral blood flow; cerebral cortex; consciousness; general anaesthetics; thalamus

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Functional brain imaging studies have been carried out to identify where neuronal activity is altered during general anaesthesia and to understand how general anaesthetic drugs impair consciousness. An important contribution of the early studies was to reveal that anaesthetic-induced unconsciousness is consistently associated with a reduction in metabolism or blood flow in the thalamus and in the midline posterior cortical areas (precuneus or posterior cingulate cortex).[1–4] These observations suggest that the thalamus and precuneus/posterior cingulate are keys to how general anaesthetics cause unconsciousness.[5–9] Decreases in blood flow in the frontal and lateral parietal cortices have also been observed during anaesthesia, but less consistently than in the thalamus and precuneus.[1–4 6–8]

Functional brain studies carry limitations that are often overlooked. They usually rely on a subtraction analysis to reveal the difference in brain activity between two

conditions: normal conscious (awake) baseline and anaesthetic-induced unconsciousness. The difficulty is to establish a causal link between the observed differences and the changes in the level of consciousness. Although functional imaging changes may reflect neural events that contribute to the loss of consciousness, there may also be changes that have nothing to do with consciousness but merely reveal non-hypnotic effects of the anaesthetic drug on the brain, such as those involving the cerebellum.[4] Distinguishing the changes that are functionally related to the loss of consciousness from those that are unrelated to unconsciousness is difficult. This limitation should not be ignored since there are still unresolved issues about the role of the thalamus and medial posterior cortices in mediating anaesthetic-induced unconsciousness.[5 9] Similarly, this problem also applies to functional brain imaging studies that attempt to identify the affected brain regions of patients who are comatose or in a vegetative state.[10]

How can we demonstrate that the changes observed with functional brain imaging during anaesthesia have anything to do with the loss of consciousness? This challenge may be addressed by using physostigmine (a centrally acting anticholinesterase) to restore consciousness during anaesthesia with propofol, thereby changing the level of consciousness while the anaesthetic concentration remains the same.[11] Thus, changes common to comparisons of anaesthesia *vs* normal consciousness and anaesthesia *vs* physostigmine-induced consciousness likely reflect neural events that are functionally related to changes in the level of consciousness since the main common feature of these two comparisons is a difference in the level of consciousness. This approach should allow us to identify the changes that are functionally linked to the difference in the level of consciousness and, importantly, control for any non-specific effects of propofol. The findings could thus further define the alterations of thalamocortical activity that contribute to (or result from) the hypnotic effect of propofol.

Methods

Subjects, design, and response to physostigmine

The study was approved by the Research Ethics Committee of the Montreal Neurological Institute. Eleven healthy right-handed subjects (20–36 yr) gave written informed consent and were tested after a comprehensive medical evaluation. Serial measures of regional cerebral blood flow (rCBF) were obtained with positron emission tomography (PET) during a single session (starting around 12:00 h and lasting about 4 h) comprising four successive periods: awake baseline (BASE), anaesthesia (subjects unconscious) (ANES), physostigmine administration (PHYSO), and recovery (20 min after end of propofol infusion) (RECO). Two scans were acquired during each period (Fig. 1A). There was an interval of at least 15 min between successive scans to allow decay of the radioactive tracer. The level of consciousness was assessed with the responsiveness component of the Observer's Assessment of Alertness/Sedation (OAA/S) scale.[12] Subjects were considered unconscious if they failed to respond to their name and to follow simple verbal commands ('open your eyes'). If the subject failed to respond, the requests were repeated three times in a progressively louder voice.

Eight subjects regained consciousness after physostigmine. The other three subjects showed no behavioural changes (Fig. 1B). Of eight subjects who regained consciousness, only four were able to remain immobile during data acquisition. The other four subjects who regained consciousness after physostigmine did not complete the study because excessive head movements during physostigmine-induced consciousness prevented data acquisition. The present results are thus for the seven subjects (six men; 20–35 yr) who completed the study: four 'responders', who regained consciousness 3–7 min after the start of physostigmine administration, and three 'non-responders', who showed no behavioural change after physostigmine. It has not been possible to recruit more subjects because clinical-grade physostigmine is no longer distributed in Canada.

We initially did not count on non-responders in the study design. Although we are aware that statistical power for group comparisons is limited by the small size of the samples, we felt that it would be preferable to include the results from the non-responders since they provide an additional opportunity to assess the role of the observed changes of rCBF in regards to the level of consciousness. No major difference between responders and non-responders is expected for the BASE–ANES contrast, which includes a difference in the level of consciousness for both groups. We expect, however, that the differences between responders and non-responders in the PHYSO–ANES contrast will reveal the critical regions implicated in the change in the level of consciousness since the contrast involves a change in the level of consciousness only in the responders.

We attempted to study the effect of physostigmine on rCBF when administered to an awake, non-medicated subject. Two subjects were tested. Despite the co-administration of glycopyrrolate to prevent the peripheral muscarinic side-effects of physostigmine, both subjects experienced intense nausea and retching that made scanning impossible. Attempts with other subjects were not undertaken given the intensity of the emetic symptoms.

Anaesthesia and drug administration

Subjects were under the care of two anaesthesiologists and one nurse. Vascular catheters were inserted under local anaesthesia in a vein of the right forearm for drug administration and in the left radial artery for blood sampling. Monitoring included ECG, pulse oximetry, intra-arterial pressure, and online concentration of oxygen and carbon dioxide in inspired and expired gas. Subjects breathed spontaneously and received supplemental oxygen via a facemask. Gentle chin lift was applied during anaesthesia to ensure patency of the airway.