Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Brown EN, Lydic R, Schiff ND, et al. General anesthesia, sleep, and coma. N Engl J Med 2010;363:2638-50.

Glossary of Terms

Anteriorization: An EEG pattern of general anesthesia usually observed in a deep state of general anesthesia characterized by alpha and delta activity that is greater in the anterior EEG leads relative to the posterior leads.

Brainstem death: An irreversible loss of all functions of the entire brain, such that the body is unable to maintain respiratory and cardiovascular homeostasis. It is identified by the total loss of brainstem function including the inability of a patient to respond to an apneic oxygen test.

Burst suppression: An EEG pattern characterized by periods of isoelectric activity interspersed with high frequency activity. As the level of general anesthesia deepens, the periods between bursts lengthens, and burst suppression changes into an isoelectric pattern. Burst suppression is also seen in anoxic coma and certain types of epilepsy.

Consciousness: The state of full awareness of self and one's relationship to the environment. It requires arousal and cognition.

Electroencephalogram oscillations: The oscillatory patterns on the EEG are measured in cycles per second or Hertz (Hz) and are characterized in terms of 5 different frequency bands: delta (0-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (13-25 Hz), gamma (40-80 Hz).

Emergence: Process through which a patient is allowed to come out of the state of general anesthesia. Muscle relaxation is reversed and delivery of the anesthetic agents is terminated. The patient is allowed to reassume control of his/her physiological functions and to recover consciousness.

Hypnotic: An anesthetic drug used that renders a patient unconsciousness.

Induction: The process by which a patient is transformed from being awake to unconsciousness to start the process of general anesthesia. This is usually achieved by administering a bolus dose of a hypnotic drug.

Inhibitory interneuron: An inhibitory interneuron, also termed a relay, association or local circuit neuron, is a multipolar neuron which connects an afferent and an efferent neuron in a neural circuit. Activation of an inhibitory neuron leads to hyperpolarization of the post-synaptic membrane of the efferent neuron, making it less likely for the efferent neuron to transmit an action potential.

Interscalene block: An approach to providing regional anesthesia to the brachial plexus for the upper extremity achieved by inserting the needle between the anterior and middle interscalene muscles at the level of the six cervical vertebra.

Isoelectric: An EEG pattern in which the EEG signal is flat, i.e., with zero amplitude. The isoelectric EEG is seen in deep states of general anesthesia, coma, brain death and during total circulatory arrest.

Maintenance: Process of sustaining a state of general anesthesia that is adequate for the surgical or medical procedure which the patient is undergoing.

Minimally conscious state: A condition of severely impaired consciousness in which intermittent but definite behavioral evidence of self or environmental awareness is demonstrated.

Paradoxical excitation: A behavioral state observed at low doses of an anesthetic drug characterized by purposeless movements, incoherent speech, with euphoria or dysphoria and an increase in EEG beta activity.

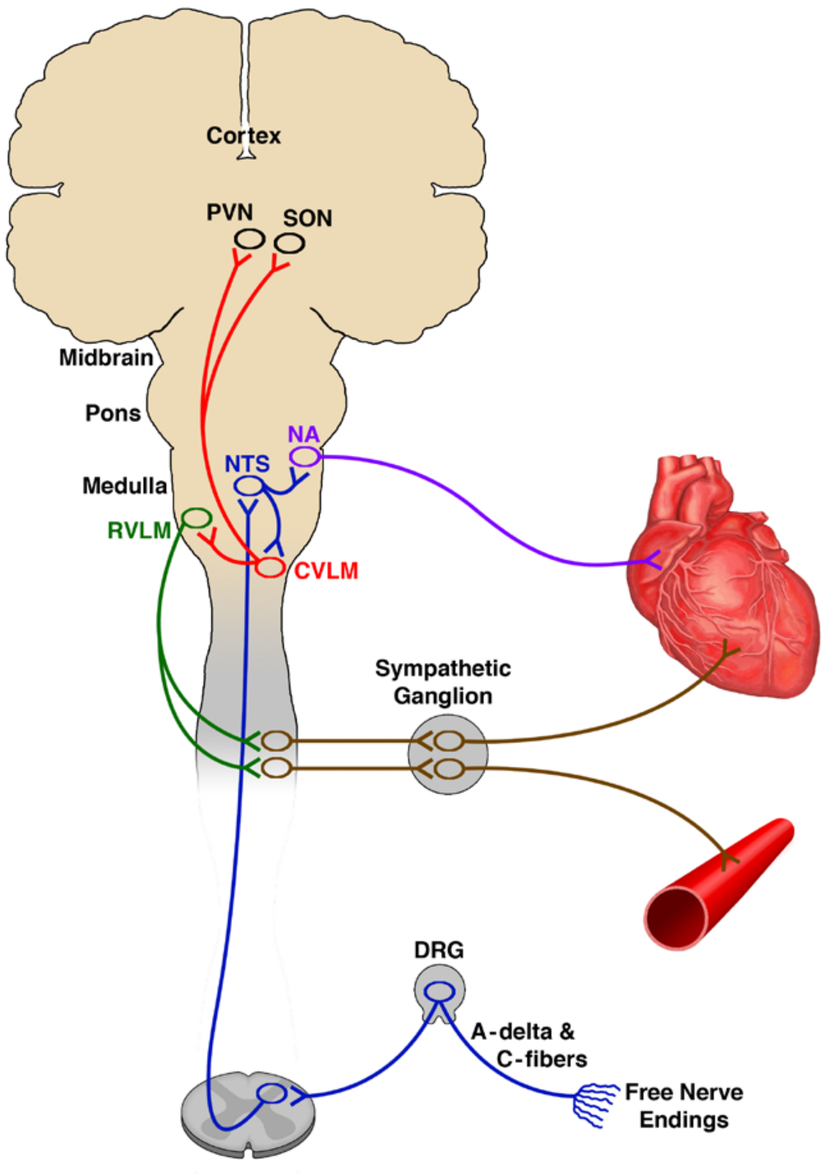
Sedation: A drug-induced state of decreased arousal, anxiolysis and decreased movement, with delayed and/or inappropriate responses to verbal commands.

Somnogen; An exogenous or endogenous substances that promotes sleep. Examples of endogenous substances are adenosine, melatonin and prostaglandin D_2 .

Monitoring Level of Arousal with the Nociceptive Medullary Autonomic Circuit

The heart rate and blood pressure changes observed in anesthetized patients in response to a nociceptive stimulus can be explained in terms of the nociceptive-medullary-autonomic circuit comprised of the spinoreticular tract, the brainstem arousal circuits, and the sympathetic and parasympathetic efferent pathways (Fig. S1). The activity in this circuit is rapidly observable under general anesthesia, as it is a fundamental component of the "flight or fight" response.[1, 2] Clinically, anesthesiologists use this circuit as a sentinel for detecting nociceptive stimuli that may lead to autonomic, stress and arousal responses. Heart rate and blood pressure changes are important markers of nociceptive information under general anesthesia because motor responses are often blocked by muscle relaxation. Inhibition of activity in the nociceptive-medullary-autonomic circuit by a hypnotic or analgesic decreases arousal and contributes to unconsciousness. Neurologists regularly test the nociceptive-medullary-autonomic circuit with nociceptive stimuli such as sternal rubs, and nail bed and total body pinches to assess the arousal levels of patients with brain injuries. [3, 4]

The nociceptive-medullary-autonomic and sleep circuits help explain why patients suffering from pain in an extremity or from labor often fall asleep or need little or no sedation for surgery after placement of a regional block. The block terminates almost immediately the nociceptive and afferent sensory[5] arousal signal. Persistent pain causes sleep deprivation which is associated with accumulation of adenosine in the basal forebrain[6] It is plausible that in these patients, both ablation of the nociceptive arousal signal and the accumulation of adenosine promote sleep.



Supplemental Figure S1. Nociceptive Medullary Autonomic Circuit. The ascending nociceptive (pain) pathway begins with A-delta and C peripheral afferent fibers that synapse in the dorsal horn on projection neurons (PN). The PNs synapse at multiple sites in the brainstem including the nucleus of the tractus solitarius (NTS) in the medulla. The autonomic response to a nociceptive stimulus is initiated from the NTS which mediates sympathetic output through the rostral ventral lateral medulla (RVLM) and the caudal ventral lateral medulla (CVLM) to the heart and peripheral blood vessels through projections to the thoracolumbar sympathetic ganglia. The NTS also projects to the periventricular nucleus (PVN) and supraoptic nucleus (SON) in the hypothalamus. The parasympathetic output is mediated through the nucleus ambiguous (NA) which projects through the vagus nerve to the sino-atrial node of the heart. The NMA circuit explains why rises in heart rate and blood pressure are used by anesthesiologists as an indicator of a change in nociceptive processing and possibly, an inadequate level of general anesthesia.

References to Online Supplement

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