Neural Synchrony, Axonal Path Lengths and General Anesthesia: A Hypothesis

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Despite decades of research, the mechanism by which general anesthetics produce loss of consciousness remains mysterious. A clue may be provided by the evidence that synchronous firing of cortical neurons underlies higher forms of neural processing. In order for these synchrony codes to be precise, transmission time must be independent of path length over all the connected sites between any two cortical areas. Since path lengths vary, developmental mechanisms must compensate for the resulting delay variations. Delay variations could be detected by spike-timing dependent cues and compensation implemented by systematic changes in axon diameter, myelin thickness or internodal distance. Anesthetics have been shown to increase conduction velocity in myelinated fibers and may therefore disrupt path-length compensation by changing velocities by different amounts in different types of axon. This simple and testable theory explains why anesthetics interfere selectively with higher cognitive functions, but leave those dominated by rate-based firing relatively intact. NEUROSCIENTIST (9)6:440-445, 2003

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Despite decades of research, the mechanism by which general anesthetics produce loss of consciousness remains mysterious. A central problem is that anesthetics are an exceptionally diverse group of substances that interact with neural tissue in equally diverse ways. Which of these interactions is critical remains uncertain, despite a long history of speculation (Caton and Antognini, 2003). The answer is likely to shed light on the neural correlates of consciousness, inasmuch as the primary effect of low doses of anesthetics on the nervous system is a rapid loss of consciousness and voluntary movement, while most other neural functions, for example axonal conduction, synaptic transmission and the response characteristics of neurons in the primary sensory cortical areas, are left largely unchanged. The substantial body of neurophysiological data that has been obtained from anesthetised animals bears witness to this. In addition, other signs of neurological disturbance such as hallucinations, abnormal motor behaviours and retrograde amnesia are mostly absent, even though these commonly accompany disturbance of consciousness produced by drugs or other generalized assaults on the brain.

The observation (Meyer, 1937) that the potency of a wide range of anesthetics correlates well with the oil-water partition coefficient (the Meyer-Overton rule: Figure 1) strongly suggests that interactions with lipid membranes are critical in causing a loss of consciousness. But since axonal conduction and synaptic transmission are relatively unaffected by general anesthetics the changes in lipid properties must be subtle and it has never been clear how such effects might cause anesthesia. Current theories are instead focussed on the interactions of anesthetics with receptors, in particular the fact that the actions of $GABA_A$ receptors are potentiated (Thomson and Wafford, 2001). It is possible that increased inhibition within certain brain centers might depress activity in ways that lead to loss of consciousness. Alternatively, changes in $GABA_A$ receptor function could disrupt oscillatory networks or other complex neural interactions essential for conscious perception.

While these, or related, receptor-based hypotheses may turn out to be relevant to many of the physiological effects of anesthetics, I want to suggest a simpler mechanism by which anesthesia may be produced, one which connects *a*) the Meyer-Overton rule, *b*) an overlooked observation on the effects of anesthetics on axonal conduction velocity (Rosner and others, 1971), *c*) the diverse range of effects of anesthetics on neural tissue and *d*) current theories on the role of synchrony in higher cortical functions. In

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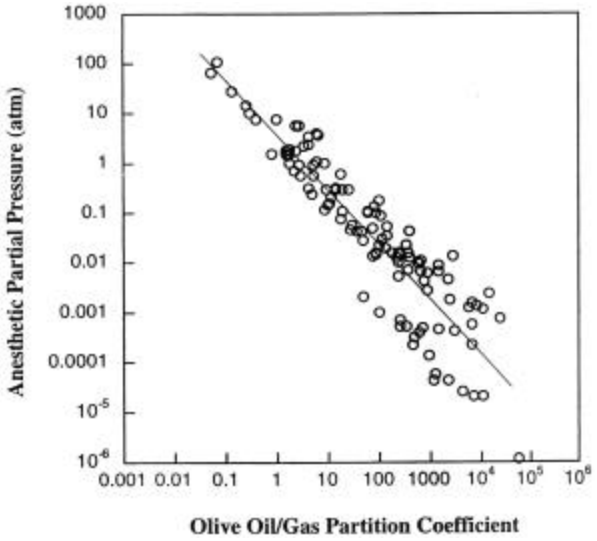

Fig. 1. Relationship of anesthetic potency vs. the olive oil/gas partition coefficient for a large number of gaseous anesthetics (from Sandberg and Miller, 2003).

brief, I propose that anesthetics disrupt neural synchrony codes that are essential for higher forms of neural processing, including those aspects that are responsible for consciousness. I suggest that this disruption occurs as a result of differential changes in the conduction velocity in axonal fibers of different diameter. These ideas, and the evidence behind them, will be expanded upon in the following paragraphs.

Neural Synchrony

There has been increasing interest in, and accumulation of evidence for, the possibility that very precise spatio-temporal patterns of firing among groups of neurons that may be in widely distant parts of the cortex may underlie the neural computations essential for higher level perception of complex objects (Abeles, 1991; Engel and others 1997, 1999; König and others, 1996; Singer and Gray, 1995; Singer, 1999; Usrey and Reid, 1999). One possible role of synchrony is that it constitutes a code that signals that disparate low-level features coded by individual neurons in different brain regions belong to the same object (von der Malsburg and Schneider, 1986). In order for it to constitute a code, receiving neurons in some area must be able to detect the synchrony present among the lower-level feature detecting neurons. More generally, a fundamental operation of cortical neurons may be to detect the synchronous arrival of sets of impulses from neurons in a number of other cortical areas, and to respond with an action potential (Softky, 1995). For large numbers of inputs and large time windows such behaviour is almost guaranteed to be true of any nerve cell; what is less certain is whether a fundamental operation is the detection of a relatively small number of inputs (e.g. 5 – 100) occurring within a time window, Δt_c, that is short compared to the average inter-spike interval (König and others, 1996), i.e. of the order of a few milliseconds or less in duration. It is assumed here that for a critical subset of cortical neurons, if not all of them, the integration time window is of the order of one or two milliseconds or less. Although this is speculative, it is not unreasonable: if the detection of synchronous inputs is a fundamental step in neural computation there would be enormous selection pressure to make Δt_c short, given the need for organisms to respond quickly to complex sensory events. Alternatively, if Δt_c is longer in individual neurons, it may nevertheless be the case that the proper functioning of distributed networks of neurons in the cortex depends on the maintenance of timing relations that are less than Δt_c. For the purposes of the hypothesis being presented here, it is necessary to assume only that millisecond scale timing relations between neurons are important: the hypothesis is also compatible with functions of synchrony other than those, such as feature binding, that have been proposed.

Many pieces of evidence point to the importance of millisecond-scale timing in neurons. *In vitro* studies show that cortical neurons are capable of firing impulses with a temporal precision of 1 ms or less in response to repeated patterns of stimulation (Mainen and Sejnowski, 1995; Nowak and others, 1997). Hippocampal CA1 pyramidal neurons can fire in response to synchronous inputs to nearby basal dendrites with sub-millisecond precision (Ariav and others, 2003). Neurons in some sub-cortical areas are also capable of detecting differences in the time of arrival of inputs to their dendrites with sub-millisecond precision. For example, humans use temporal differences as small as 10 µs to binaurally localize sound sources (Hafter and others, 1979). Neurons in the nucleus laminaris of the owl are sensitive to temporal delays of 20 – 30 µs (Moiseff and Konishi, 1983) and individual neurons in guinea pig inferior colliculus can discriminate 30 µs delays (Shackleton and others, 2003). Neurons in the brain of the fly *Ormia* have the even more remarkable capacity to detect temporal delays of around 50 ns (Mason and others, 2001).

Although these neurons and their associated circuitry are possibly specialized and atypical, the sub-millisecond precision of some cells suggests that millisecond precision of many cells would not be difficult to achieve. Recently, spike timing has been shown to be a critical factor in synaptic plasticity: changes in the relative timing of pre and post-synaptic action potentials on a timescale of tens of milliseconds (and possibly less) are critical in determining whether inputs are potentiated or depressed (Bi and Poo, 1998; Markram and others, 1997).

Maintaining Synchrony by Path-Length Compensation

A corollary of a narrow integration time window, or high temporal sensitivity, is a need for axonal path-length compensation. Because of the presence of topographic maps in the cortex, signals representing different low-level features (e.g. edges in a visual image) will often arise in physically different parts of a given cortical area. If these signals are to be permuted in different ways in a higher level area, using a temporally precise code, then conduction times from the lower area to the higher area need to vary by less than Δt_c (Figure 2). This will not be a problem if conduction velocities are sufficiently fast, or if path lengths between all connected pairs of points in two areas are sufficiently similar. However it is probable that neither of these conditions is generally true. Conduction velocities of white matter axons are in the range 1.5 – 7 m/s for both feedback and feedforward connections between V1 to V2 in the monkey (Girard and others, 2001). Path length variations between cortical areas have not been characterized, but given known patterns of connectivity (Figure 3) they can be estimated to be of the order of the size of a single cortical area e.g. 5 – 15 mm in the monkey. Lower and upper temporal delay variations given by these figures are in the range of 1 to 10 msecs. Larger delay variations will occur if signals from different areas, rather than different regions within an area, need to be combined in a temporally precise way in a third area (Figure 4). It is interesting that conduction velocities appear to scale with brain size in such a way that mean cross-brain conduction times are similar for a variety of brains (Shultz and Wang, 2001). In the rat, the velocity of conduction between areas 17 and 18a has been estimated to be 0.5 – 1.2 meters/second (Nowak and others, 1997) which is consistent with a 3 – 4 fold difference in size between rat and monkey brains. Path length variations should also scale with brain size. The impact of path length variations on temporal delays should thus be similar in brains of different size.

The fact that axons can function as delay lines, and the need for path-length compensation in situations where synchronous arrival of impulses is important, has long been recognised (see Waxman, 1975, for review). Indeed there is now a substantial amount of evidence for path-length compensation in a variety of species and brain regions. For example, in the squid *Loligo*, the distances between the central command nucleus and the muscles in the mantle, which mediates the escape reflex, are unequal. Pumphrey and Young (1938) showed there was a relation between the diameter of the axons innervating the mantle muscles and their length, such that synchronous contraction of the mantle would ensue following activation of the command nucleus. More recently, nearly equal response latencies in the face of unequal path lengths have been demonstrated between the ventrobasal nucleus of the thalamus and somatosensory cortex in the mouse (Salami and others, 2003); between the inferior olive and cerebellum in the rat (Sugihara and others, 1993; Lang and Rosenbluth, 2003) and between the amygdala and perirhinal cortex in the cat (Pelletier and Paré, 2002). In these cases compensation is able to achieve latency variations of a few milliseconds or less in the face of two-fold length variations, and appears to be produced by a correlation between conduction velocity and path length rather than by variable synaptic delays in the target structure. To the author's knowledge path-length compensation has not been demonstrated within the cerebral cortex, but its presence in sub-cortical structures and thalamic afferents points to the probability of its occurrence in cortex as well.

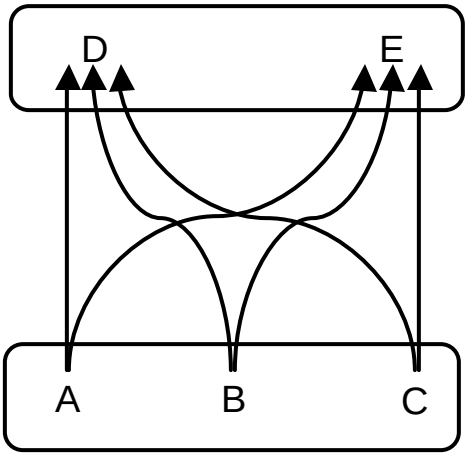

Fig. 2. The diagram depicts two cortical areas; labels A, B and C denote neurons (or groups of neurons) representing features which in combination form part of the higher level features represented by the activity of neurons D and E in two regions in a second cortical area. In order for synchronous firing of A, B and C to be detected, conduction times between the two areas need to vary by less than the integration time window for neurons D and E.

Implementing Path-Length Compensation

Mechanisms for implementing compensation include changes in axonal diameter, myelin thickness, resistance, or inter-nodal distance. It is probable that path-length compensation needs to be learnt, or refined by learning, given that the shape of the brain may not be precisely genetically specified and that it changes after birth. A suitable cue for a compensating mechanism would be the consistently late arrival of a spike relative to the times of other spikes that were successful in firing a cell. Pre-synaptic inputs that have this property become depressed (Markram and others, 1997; Bi and Poo, 1998). It can be argued that these late spikes still have a causal relation with the post-synaptic spike, since merely speeding up the afferent conduction velocity (assuming an axon of some length is involved) will lead to the situation where the post-synaptic spike follows the pre-synaptic one. Thus, in addition to depression, the response to delayed

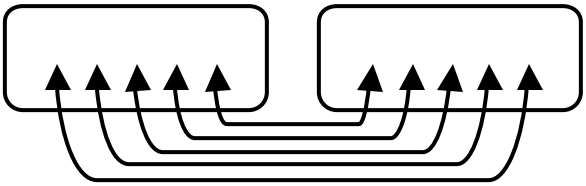

Fig. 3. Patterns of connectivity between adjacent cortical areas in the visual system can be inferred from a knowledge of the retinal topography. It is common for mirror reversals in topography to occur at areal boundaries and this means that connections lengths must vary.

spikes may include a retrograde signal that causes an increase in conduction velocity in the afferent axon. In this context it is interesting to note that myelination occurs late in brain development, and in humans is not complete until 5 or more years of age. Disorders of myelination are frequently associated with mental retardation. Both these observations suggest that myelination is regulated by functionally related factors and that this regulation is essential for normal brain development.

Effects of Anesthetics on Axonal Conduction Velocity

In spite of the long history of research inspired by the Meyer-Overton correlation on the interactions between anesthetics and lipid membranes, it is surprising that very few studies of the effects of anesthetics on conduction velocity appear to have been done. A literature search revealed only two. One (Mikulec and others, 1998) showed no effect of halothane on conduction velocity in Schaffer collaterals in hippocampal tissue slices at room temperature. The other (Rossner and others, 1971) showed, remarkably, that a variety of anesthetic agents caused 10 – 20% increases in conduction velocity in peripheral nerves of human volunteers. Although these results need to be confirmed, the magnitude of the changes is large, and it seems odd that the implications have been overlooked. The finding is not inconsistent with other observations showing that anesthetics increase membrane volume and probably membrane thickness (Kita and others, 1981); the latter would lead to a decrease in membrane capacitance and this would be expected to lead directly to an increase in conduction velocity (Waxman, 1980; Jack and others, 1983). However many other factors occurring as a secondary consequence of changes in membrane conformation, including changes in trans-membrane resistance, changes in the properties of nodal membrane and effects on nodal Na^+ channels (Haydon and Urban, 1983) could equally well play a role.

A proportional increase or decrease of the same amount in conduction velocity of all fibers would leave timing relations unchanged and if this happened there should be little effect on brain function (except a slight speeding up or slowing down). However the factors

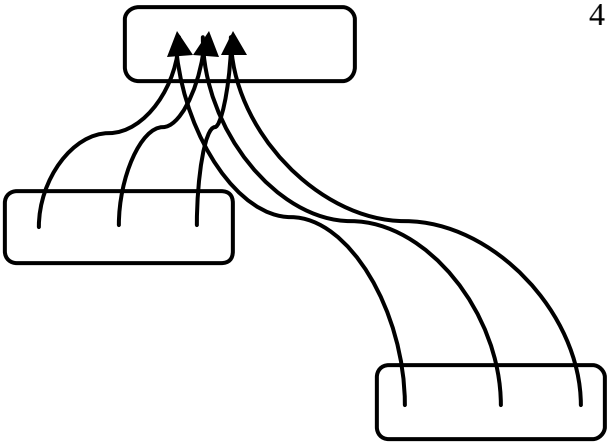

Fig. 4. Signals from two cortical areas converge, through routes of differing length, on a third area. If signals in the two areas are to be bound together by a synchrony code, a path-length compensation mechanism may be needed to ensure that conduction times along the two pathways are similar.

that determine conduction velocity in myelinated axons are complex. They include axonal diameter, thickness of the myelin sheath, inter-nodal distance, myelin resistance, capacitance, and the channel properties of nodal membrane (Waxman, 1980). It is *a priori* unlikely that, if anesthetics change conduction velocity, they will do so by the same proportion in fibers of different type. It is worth noting that fiber diameter in white matter varies by about an order of magnitude and it is not known what the determinants or correlates of this variation are. Given this, it is proposed here that general anesthetics produce loss of consciousness by differentially changing conduction velocity among different classes of myelinated axons, which in turn leads to a disruption of neural synchrony codes essential for the integrated function of cortical areas.

Discussion

Strengths

Although speculative, the hypothesis provides a simple explanation of why anesthetics quickly and reversibly interfere with higher forms of mental activity, including consciousness, while leaving (at low doses) synaptic function and other, rate based, forms of neural processing relatively intact. Other hypothesised mechanisms, in particular those based on interactions with specific receptors such as the $GABA_A$ class, are (necessarily) vague as to why these interactions would lead directly to loss of consciousness, and do not easily explain the absence of system-specific behavioural neurological signs that are usually associated with receptor-specific drug actions. Reconciling receptor-specific theories with the Meyer-Overton rule is also difficult (Sandberg and Miller, 2003). The explanation suggested here does not have these problems. It is consistent with the Meyer-Overton rule inasmuch as it is hypothesised that the critical site of action of

anesthetics is on myelinated axons. The target within the axon might equally well be the node of Ranvier, the myelin sheath, or both. One attractive possibility is that anesthetics increase pressure within the membrane, forcing the bilayer apart and decreasing membrane capacitance. This explanation is also consistent with the remarkable observation that anesthesia can be reversed by pressure (Miller and others, 1973) since this would be expected to restore membrane thickness to its normal value. It is also consistent with the inability of any known pharmacological agent to reverse anesthesia: receptor-based theories predict that such agents ought to exist.

Objections

An obvious weakness of the theory is that there is no evidence that anesthetics.produce differential changes in conduction velocity in different classes of axon. However there is also no evidence that contradicts this idea, and it should not be difficult to test it experimentally. Additional objections could be made, as follows:

1. the effects on timing may be too small to be significant, since they depend on differential changes in conduction velocity. These differences may be too small to have an effect on timing relations that is significant relative to the temporal integration window. For example, assume that the (compensated) conduction delay between two areas is 10 msecs. Suppose the differential velocity changes in two components of the pathway are 5% and 15%. This introduces a temporal asynchrony of only 1 msec between the two pathway components. This argument cannot be evaluated because the temporal precision of timing relations in the cortex is unknown. However, as pointed out above, neurons are able to make exquisitely precise sub-millisecond or even sub-microsecond temporal discriminations in some circumstances, and a general level of millisecond scale precision does not seem unlikely. Of course if the theory can be shown to be correct by other means, it should be possible to estimate the level of temporal precision required by higher-level neural functions by measuring the degree of de-synchrony produced by anesthetics.
2. Anesthetics produce immobility akin to anesthesia in very small animals, such as *Drosophila* and *C. elegans*, where it seems unlikely that path-length compensation will be needed. They do this at doses comparable to those producing loss of consciousness in humans. It is not inconceivable that many, or all, nervous systems make use of precise timing information and an argument based on scaling might be used to relate the fly's brain to that of larger mammalian ones (especially given the nanosecond precision of *Ormia*). However it is hard to believe that precise timing would be important in an animal like *C. elegans*. At higher doses anesthetics can block axonal conduction and depress synaptic transmission and it is possible that invertebrates are more susceptible to these effects than are vertebrates.
3. There are exceptions to the Meyer-Overton rule: some substances predicted to be anesthetics on the basis of their lipid solubility are not (Sandberg and Miller, 2003). For example, some anesthetic enantiomers vary in their anesthetic potency but not in their lipid solubility. Potency in these cases can be shown to correlate instead with the interaction with specific neurotransmitter receptors (Thompson and Wafford, 2001). While these observations point towards receptor-specific rather than membrane-specific effects of anesthetics it is possible that changes in receptor function are secondary to changes in membrane conformation and that some substances can dissolve in lipids in ways that affect neither membrane conformation nor conduction velocity. Alternatively, it may be that the relevant receptor interactions contribute directly or indirectly to changes in conduction time, or cause variations in synaptic transmission time which have the same end result of synchrony disruption.
4. Temperature increases conduction velocity, by about 5% per degree centigrade (Waxman, 1980) but neither moderate hypo- nor hyper-thermia produce anesthesia: consciousness survives a range of body temperatures from about 30ºC to 40ºC. However interactions between fiber diameter and the effects of temperature on conduction velocity in myelinated axons have not been reported. As argued above, proportional changes in conduction velocity that are the same in fibers of different diameter ought not to disrupt delay-length compensation mechanisms and thus ought not to produce anesthesia.

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