Some heightened sensitivity

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With the progressive ageing of the population, anaesthetists are increasingly faced with geriatric patients. As our patient populations grow, there have been regular calls to limit anaesthetic exposure in older patients out of fear of overdose. The current concern regarding postoperative cognitive dysfunction weighs heavily on some patients’ minds, while anaesthetists ponder the significance of the ‘triple low’ as a predictor of morbidity and mortality.1,2 Anecdotally, elderly patients take a variable, but prolonged, amount of time to recover from anaesthesia relative to younger patients. The open question remains, how and

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why is the older brain different in its response to and recovery from anaesthetics?

One possibility is that the older brain is simply more sensitive to anaesthetics; lower doses are required to achieve the same effect. The minimal alveolar concentration (MAC) of volatile anaesthetic required to inhibit movement in response to a surgical stimulus decreases with age. Yet a series of elegant experiments in ruminants, which have separable cerebral and vertebral circulations, demonstrated that MAC correlates with concentrations of anaesthetic in the spinal cord rather than with cortical processing, so it is unclear whether the change in anaesthetic sensitivity responsible for the age-related decline in MAC includes a cortical effect. Elderly patients are also more sensitive to propofol for induction. It is worth noting, however, that in at least one study older rats required higher brain concentrations of propofol to induce 1 s suppressions on EEG, despite lower serum propofol levels than were present in younger rats.7

In this issue of the British Journal of Anaesthesia, Chemali and colleagues report on the results of a series of experiments measuring the effect of ageing on anaesthetic sensitivity in the line of Fischer 344 rats maintained by the US National Institute on Aging. Paralleling previous work on age-adjusted MAC, the authors found that young adults were significantly less sensitive to isoflurane than older animals (recovering the righting reflex at lower steady-state concentrations of anaesthetic). Moreover, older rats took a longer and more variable time to recover both from isoflurane and from a single bolus dose of propofol. As ageing can affect a number of physiological parameters, including cardiac output, functional residual capacity, and body composition, it is unclear whether the prolonged recovery is the result of some combination of a change in clearance, distribution, and the central response to the anaesthetic. Finally, the authors demonstrate that methylphenidate, a centrally acting catecholamine reuptake inhibitor, can speed the recovery of older rats to be faster than that of young rats not exposed to methylphenidate.

The major advance of Chemali and colleagues is the application of a measure of cortical burst suppression derived from the EEG, which demonstrates that the change in anaesthetic sensitivity is present in brain. To avoid confounding from the declining voltage amplitude in the EEG signal with ageing, the authors developed a sophisticated measure to detect burst suppression rather than the routine voltage threshold of 10 μV. This was used to build a time-varying estimate of the probability that the animal was in burst suppression. By developing a continuous, quantitative measure of cortical suppression, the authors are able to show that, at a steady state of isoflurane, aged rat cortex is more sensitive to isoflurane. This demonstrates that the behavioural sensitivity change is a pharmacodynamic rather than only a pharmacokinetic effect. Finally, the cortical recovery time frame from propofol parallels the behavioural results, suggesting that the prolonged effect of propofol is attributable to increased cortical sensitivity.

It is currently unclear what mechanism might underlie a change in global sensitivity to anaesthetics. Both propofol and isoflurane have some γ-aminobutyric acid (GABA)ergic effects, but it is unclear from the present work whether this effect is mediated by some effect on GABA receptors or via another system. On the one hand, mice expressing an isoflurane-resistant knock-in α1 GABA<sub>A</sub> receptor subunit did not change either MAC or the suppression of neuronal responses to noxious stimulation. Yet sensitivity to other GABAergic sedatives, including methohexital and midazolam, also increases with ageing. Perhaps ageing-related changes in GABA<sub>A</sub> receptor subunit expression or other, compensatory modifications that occur with ageing could explain the increased sensitivity to anaesthetics in older animals. Alternatively, there could be some downstream effect of ageing that explains a generic increase in sensitivity to sedative medications.

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Fig 1 (a) Curves reflecting different anaesthetic sensitivities, where the anaesthetic concentration at which the probability of being anesthetized is 50% (EC<sub>50</sub>) for two populations differs by a factor of 100. The population depicted by the blue curve is less sensitive to anaesthesia, and hence remains awake at anaesthetic concentrations that render the Green population unconscious. In the experiment of Chemali and colleagues, the Green curve corresponds to older rats and the blue curve to younger rats. (b) First order drug kinetics yield an exponential decline in effect site concentration over time. (c) A sensitivity shift with first order drug kinetics predicts longer time to emergence, with broader distribution of emergence times. We simulated 10,000 animals emerging from anaesthesia with both sensitivity relationships in (a) and with the effect site concentration from (b). The distribution of times to waking for the young, less sensitive population (blue) was shorter and narrower than the distribution of times for the aged, more sensitive population (Green). (d) Emergence is not the reverse of induction. During induction, the organism is less sensitive to anaesthetics than during emergence. A simple model to explain hysteresis is that the brain tends to stay in its current state, as though it is trapped in a potential energy well. The probability of switching states is a function of the height of the barrier above the bottom of the well. The arrows show induction (Green) and recovery from anaesthesia (blue) that correspond to the transition from one energy well to the other. Note that these transitions do not occur at the same anaesthetic concentration. This minimal model is consistent with the results of Friedman and colleagues.
As Chemali and colleagues\(^8\) demonstrate, the anaesthetic state depends upon a balance of cortical suppression and the various arousal systems of the brain. The same group has previously demonstrated that the ‘reanimation’ observed with systemically administered methylphenidate parallels the effect of stimulating the dopaminergic ventral tegmental area. Perhaps the tone of the dopaminergic system sets the anaesthetic sensitivity of the brain, and declining dopaminergic tone with ageing causes increased anaesthetic sensitivity; this would certainly be a parsimonious explanation with obvious appeal.

This minimal model of anaesthetic sensitivity makes several predictions that can be tested against the data presented in the report by Chemali and colleagues.\(^8\) Begin by assuming that ageing shifts the sensitivity curve to the left and methylphenidate moves it back to the right (Fig. 1a). If we look at the mean recovery times, this simple model does surprisingly well. Yet one very salient feature in the recovery time data of Chemali and colleagues,\(^8\) presented in their Figure 1, is that the spread of the recovery times decreases as the recovery times shorten; an alternative way of saying this is that the variance of the distribution decreases as the mean decreases.

Can we capture this spread in the recovery times with this minimal model of sensitivity changes? If recovery from anaesthesia were simply a probabilistic sigmoidal function of effect site anaesthetic concentration, one would not expect any difference in the width of the distribution of times to recovery with a change in sensitivity. Yet the simple addition of first order kinetics to effect site concentration (Fig. 1b) leads to a much slower transition through the steep portion of the dose–response curve for the more sensitive population, which will produce a wider distribution of times as the average recovery time increases (Fig. 1c). Our toy model is doing surprisingly well.

One observation from the data of Chemali and colleagues,\(^8\) in their Figure 1, however, stands in stark contrast to our model prediction. For all groups except the older rats given methylphenidate, the amount of variance in the time to recovery changes in parallel with the mean time to recovery. The recovery times in aged rats given methylphenidate are less variable than in aged rats given only propofol, but substantially more variable than in younger rats given only propofol, which take longer to wake. Yet our simple model that combines a sensitivity change with pharmacokinetics would predict the variance in older rats given methylphenidate to lie between the young rats given propofol only and the young rats given propofol and methylphenidate. The failure of this prediction suggests that age-related shifting of the dose–response curve of general anaesthetics that is opposed by methylphenidate within a single pathway is insufficient.

Indeed, even the careful characterization of anaesthetic sensitivity by Chemali and colleagues\(^8\) is incomplete. Kelz’s group have definitively demonstrated that recovery from anaesthesia is not simply attributable to washout of anaesthetic agent, because the sensitivity curves for induction and recovery are shifted versions of each other, with induction taking the role of the blue curve and recovery taking the role of the green curve in Figure 1d.\(^15\) Kelz termed this tendency for the awake brain to remain awake and the anaesthetized brain to remain anaesthetized ‘neural inertia’. Given that Chemali and colleagues\(^8\) examined only the recovery arm in their experiments, it remains an open question as to whether ageing shifts the induction curve in parallel to the recovery curve or whether the degree of neural inertia in the aged brain changes.

The presence of neural inertia is a form of state path dependence, known generically as hysteresis. A simple two-state model that can capture anaesthetic hysteresis incorporates two different energy wells, one well for the ‘awake’ state and one for the ‘anaesthetized’ state, separated by an energy barrier. The probability of crossing the barrier, one measure of anaesthetic sensitivity, is a function of the depth of the well and the kinetic energy of the particle (Fig. 1b). As the two wells can each change depth at different anaesthetic concentrations, the probability of crossing the wall in one direction need not be the same as the probability of moving in the opposite direction. The presence of neural inertia dictates that at least this minimal model is necessary to capture the brain’s sensitivity to anaesthetics. Moreover, this offers more parameters that could affect anaesthetic sensitivity to explain the interaction of methylphenidate with ageing; perhaps methylphenidate selectively affects the kinetic energy of the particle without changing the depth of the energy wells.

Developing a better predictive model of what governs behavioural state changes in the brain will require much more quantitative data. The technique used by Chemali and colleagues\(^8\) gives us more useful data points, by adding a measure of cortical suppression to overt behavioural measures. This technique can be exploited for characterizing both induction and recovery and seems to parallel the behavioural changes seen in time to recovery.

It is worth noting that there is a long way between burst suppression and wakefulness. We have previously reported that there are some characteristic features in brain activity that occur during recovery from anaesthesia, and transitions between these different states reveal a required sequence of states that appear before recovery.\(^15\) Are other EEG activity patterns that occur at intermediate anaesthetic doses also affected by ageing in the same way as burst suppression, with a shift to the left in the curve, or is there a change in the architecture of the network of brain activity states? Perhaps certain rhythms are more stable in old brains and others simply do not occur. At present, we have no sense of how ageing impacts the functional effects of anaesthetics on brain activity patterns.

Understanding how the dopaminergic and other arousal systems interact with general anaesthesia will help to inform our understanding about rational interventions to facilitate recovery from anaesthetics in ageing patients. Given that much of the concern about anaesthesia in the geriatric population could be characterized as recovery gone awry, developing and characterizing an adequate model of recovery that captures the effect of ageing is of compelling importance.

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None declared.

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2. Kertai MD, White WD, Gan TJ. Cumulative duration of “triple low” state of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia is not

The diving bell and the butterfly

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When patients undergo general anaesthesia, they might feel as if they are entering an oxygenated and carefully monitored diving bell. They entrust their lives to the anaesthetist, who lowers them gently into the depths of oblivion for the duration of the surgery, before allowing them to emerge safely with awareness restored. When patients express dread of awakening prematurely in the surgery. This finding should alter our perspectives and priorities. Anaesthetists have historically focused on the prevention of intraoperative awareness, but this research establishes the importance of our patients of distressing awareness with profound weakness that can occur after surgery. Encouraging in the findings of Thomsen and colleagues, however, was that when intraoperative neuromuscular monitoring was used, both postoperative respiratory complications and distressing postoperative awareness had a much lower incidence.

One of the earliest descriptions of succinylcholine administration to humans comes from Otto Mayrhofer, who in 1952 described his self-experiments with this depolarizing neuromuscular blocking agent. Mayrhofer extols one of the benefits of succinylcholine by stating, ‘It is destroyed in the body so rapidly—apparently by enzymatic hydrolysis—that no antidote is needed’. Mayrhofer describes his experiences of awake paralysis as follows: ‘double vision, ptosis, general muscle weakness, and intercostal paralysis, followed about 30 s later by total paralysis, including the