

endofullerenes are self-assembled chains of C₆₀. The observation of these structures raises the hope that refined processing techniques can be developed to produce them in large quantities.

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How does xenon produce anaesthesia?

Since the discovery that the gas xenon can produce general anaesthesia¹ without causing undesirable side effects, we have remained surprisingly ignorant of the molecular mechanisms underlying this clinical activity of an ‘inert’ gas. Although most general anaesthetics enhance the activity of inhibitory GABA_A (γ-aminobutyric acid type-A) receptors^{2,3}, we find that the effects of xenon on these receptors are negligible. Instead, xenon potentially inhibits the excitatory NMDA (N-methyl-D-aspartate)

receptor channels, which may account for many of xenon’s attractive pharmacological properties.

We found that xenon had virtually no effect on GABA_A receptors. Currents activated by 3 μM GABA, both in voltage-clamped cultured rat hippocampal neurons and in voltage-clamped PA3 cells⁴ that stably expressed defined GABA_A subunits, were not significantly affected even by 100% xenon (to function as a human anaesthetic, the half-maximal effective concentration (EC₅₀) is 71% v/v; ref. 5). Xenon also had little effect on functional GABA-releasing synapses in hippocampal neurons, with 80% xenon reducing peak inhibitory postsynaptic currents by only 8 ± 2%. This result indicates that the presynaptic effects of xenon must also be very modest.

Apart from the GABA_A receptor, the only generally accepted neuronal target of conventional anaesthetics is the NMDA receptor. This subtype of glutamate-activated ionotropic channels is implicated in synaptic mechanisms underlying learning, memory and the perception of pain⁶. The NMDA receptor is also believed to be a target of the intravenous general anaesthetic agent ketamine⁷, and possibly nitrous oxide⁸.

We therefore looked at the effects of xenon on NMDA-activated currents in cultured hippocampal neurons. We found that 80% xenon, which will maintain surgical anaesthesia, reduced NMDA-activated currents by about 60% (Fig. 1a), with no significant change in the NMDA EC₅₀

value or Hill coefficient. This non-competitive inhibition indicates that xenon should strongly inhibit neural transmission, despite the high glutamate concentrations in synaptic clefts.

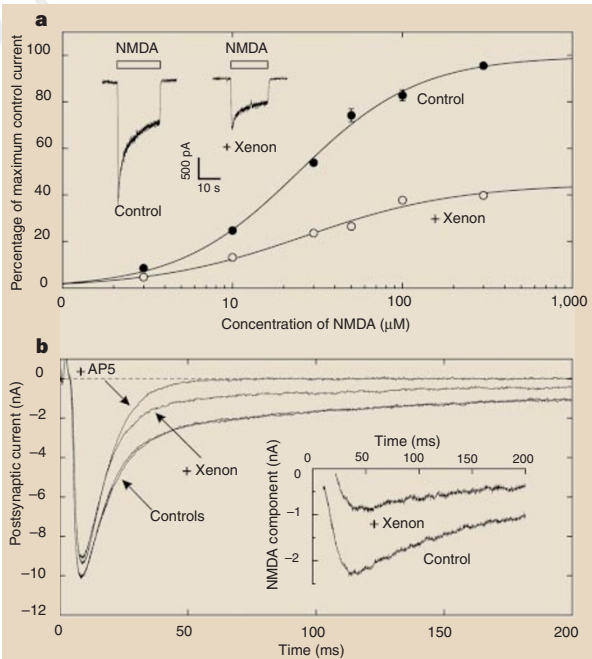
We then tested this in microisland cultures of hippocampal neurons that form synapses with themselves (autapses)⁹. A typical glutamatergic postsynaptic current recorded from a hippocampal neuron is shown in Fig. 1b. The control records show a characteristic biphasic time course, with a fast component mediated by non-NMDA receptors and a much slower component mediated by NMDA receptors. This NMDA receptor-mediated component could be readily identified as it was blocked by the highly selective competitive antagonist AP5 (DL-2-amino-5-phosphonopentanoate)¹⁰.

Addition of 200 μM AP5 almost completely blocked the slow component, leaving only a fast component, with a single exponential time course very similar to that of the control fast component. The effect of xenon on the glutamatergic postsynaptic current resembled that of AP5 (Fig. 1b). The slow, NMDA-receptor-mediated component was reduced by over 70%, whereas the fast component barely changed. So, not only did xenon inhibit synaptic NMDA receptors, it had little apparent effect on non-NMDA receptors.

If xenon exerts its effects by inhibiting NMDA receptors, then this explains some important features of its pharmacological profile, particularly as NMDA-receptor antagonists can relieve pain and cause amnesia, which are features of xenon anaesthesia. Like nitrous oxide (‘laughing gas’), which may also act, at least partly, on NMDA receptors⁸, xenon can induce a state of euphoria. Other neuronal targets for xenon may emerge, but its powerful inhibition of the NMDA receptor is likely to be instrumental in the anaesthetic and analgesic effects of this ‘inert’ gas.

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Figure 1 Xenon inhibits NMDA receptors in cultured rat hippocampal neurons. **a**, NMDA activates an inward current (in neurons clamped at -60 mV) with an EC₅₀ of 24 ± 2 μM NMDA and a Hill coefficient of 1.2 ± 0.1. Xenon inhibited the current by approximately 60% but did not significantly change either the EC₅₀ or the Hill coefficient. Each data point represents the mean peak current from at least 6 cells. Inset, typical current traces (at 100 μM NMDA) in the presence and absence of xenon. **b**, Xenon selectively inhibits the NMDA-receptor-mediated component of glutamatergic excitatory postsynaptic currents (EPSCs). Neurons were voltage-clamped at -60 mV; synaptic responses were stimulated by a 2-ms depolarizing pulse to +20 mV. Control glutamatergic EPSCs displayed a characteristic biphasic decay. The slow component was completely blocked by 200 μM AP5, leaving the fast component almost unaffected. Inset, the NMDA-receptor-mediated component (the difference between the control EPSC and that in the presence of AP5) and its size in the presence of xenon (calculated by taking the difference between the EPSC in the presence of xenon and that in the presence of AP5). Control solutions were equilibrated at room temperature with 80% N₂ and 20% O₂, and test solutions with 80% Xe and 20% O₂.



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