100 YEARS AGO

One of the latest departures of the experimental psychologist consists in prodding people with a pointed instrument when they are asleep to find out how much excitation is required before they begin to move, and how much it takes to wake them up. This method is embodied in a paper on "Experimental Investigations on the Depth of Sleep" by Drs. Sante de Sanctis and U. Neyroz, of Rome, a translation of which is given in the *Psychological Review* for May. The instrument employed is called a Griessbach ethesiometer (made by Brändli, of Basle), and may be used with either a sharp or blunt point. It measures the stimulus necessary to induce subconscious reaction, and that applied at the waking point... The [resulting] curves are all of zigzag form, and the experiments may perhaps suggest a practical application in the case of subjects who find it hard to wake in the morning, and who may overcome the difficulty by timing their sleep so that the waking point is at a minimum when they wish to rise.

From *Nature* 5 June 1902.

50 YEARS AGO

Progress in the field of sound recording was amply demonstrated in the annual exhibition of the British Sound Recording Association, held at the Waldorf Hotel, London, during May 17–18.... At long last the traditional wax cylinder for office dictating is being replaced by a plastic belt, which can be folded and sent through the post, as can also a paper disk carrying magnetic material, normally used when clamped on a turntable. In the field of commercial disk records, samples of the narrow-groove slow-speed records, which can play for a long time, have been in hand for some years, apart from talking-books for the blind; before the end of the year, two of the leading companies in this field will be making and distributing such disks. The 'battle of the revs', already in full swing in the United States, will soon be in full force in Britain also. Fortunately, many firms can supply reproducers with all three speeds, 78, 45 and 33 1/3 r.p.m., and all that the user has to take care of is the use of a needle with the correct radius of needle-tip.

From *Nature* 7 June 1952.

potentiation) and how they are removed (producing synaptic depression).

How can one study the dynamics of native AMPA receptors in neurons? The receptors alone are too small to see, even with a microscope, so Borgdorff and Choquet[1] coated tiny latex beads with antibodies that bind to the receptors. When applied to living neurons in culture, the beads adhere to AMPA receptors on the neuronal surface and act as microscopic signposts. In this way, lateral movements of the receptors can be tracked by video microscopy.

Using this approach, Borgdorff and Choquet found that AMPA receptors alternate abruptly between periods of rapid meandering (probably diffusion) on the neuronal outer membrane and periods of restricted motion within a submicrometre area ('confinement'). Confinement occurred mostly when the receptors were near synapses (which were detected with a specific dye). These findings imply that a zone of restricted diffusion exists in the neighbourhood of synapses. This 'perisynaptic' region probably contains specific anchoring proteins that bind to and tether AMPA receptors. The beads are too big to penetrate the narrow synaptic cleft, so a drawback of the approach is that it cannot sample true synaptic receptors. So we are left to presume that AMPA receptors located actually within the synapse are, like the perisynaptic receptors, also immobile.

Borgdorff and Choquet also observed that AMPA receptors sometimes moved from the vicinity of one dye-stained synaptic region to another. Whether this occurs *in vivo* is unclear. Normally, surface AMPA receptors undergo internalization (endocytosis), in which a patch of receptor-containing membrane is pinched off into the neuron as a tiny sac. Internalized receptors are then recycled back to the surface by secretion (exocytosis), in which the internal sacs fuse with the plasma membrane[5,6]. The attachment of a latex bead to surface AMPA receptors is expected to prevent endocytosis; indeed, the authors found that abortive endocytosis seemed to account for a small minority of confinements. So perhaps the propensity to move from one synaptic region to another is exaggerated by the prolonged lifetime of bead-attached AMPA receptors on the neuronal surface.

More significantly, Borgdorff and Choquet showed that the surface mobility of AMPA receptors is influenced by intracellular calcium ions. The authors evoked a localized increase in calcium concentration in neurons by using a laser beam. In response, nearby AMPA receptors rapidly became immobilized, and this immobility persisted after the calcium spike. As postsynaptic calcium increases are a cardinal feature of excitatory synaptic transmission, calcium-dependent immobilization might explain why AMPA receptors accumulate at synapses. A large postsynaptic increase in calcium concentration is also a well-known signal for strengthening of synapses, so, more interestingly, this could also be a mechanism for gathering more AMPA receptors in synapses to potentiate the postsynaptic response. Indeed, Borgdorff and Choquet observed that repeated calcium increases led to a local accumulation of AMPA receptors on the neuronal surface. But it remains to be seen whether surface AMPA receptors accumulate in response to postsynaptic calcium increases under more 'natural' conditions — that is, after synaptic stimulation.

Until now this field has focused on the idea that the delivery of AMPA receptors to synapses is regulated by exocytosis from internal compartments in the neuron[6,7]. The study by Borgdorff and Choquet[1] points to another possibility, involving the lateral movement of surface receptors from extrasynaptic sites. The idea is supported by an earlier study of a mouse mutant called Stargazer, which shows neurological defects[8]. This study suggested that a critical step in synaptic delivery occurs after AMPA receptors reach the cell surface. More recently, another major subtype of glutamate receptor, the NMDA receptor, has been shown to move laterally from extrasynaptic to synaptic sites[9]. So a dynamic surface distribution might be a universal property of synaptic receptors.

What molecular mechanisms underlie the controlled lateral mobility of AMPA receptors? Presumably, it has something to do with calcium-regulated interactions between the receptors and intracellular anchoring proteins. More generally, how do synapses and synaptic circuits in the brain maintain consistent properties in the face of such molecular flux (assuming that it occurs *in vivo*)? The answer to this question is a long way off, but it is clear that the more we probe the molecular workings of synapses, the more we can understand their dynamic organization and their readiness for rapid change. ■

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