gravitational constant, G, has to vary in inverse proportion to the time that has elapsed since the origin of the universe, defined in the Friedmann sense. Although Sir Fred admitted that he had always doubted this variability of G, which of course was proposed by Dirac in 1937, he felt that the time was now ripe for a re-examination.

The time variability of G would, for example, have a marked effect on the life-cycles of stars whose speed of evolution at some stages is strongly dependent on G. Larger values of G in the past mean that stars will have evolved faster than is normally supposed from present observations, and this would have many profound implications for astronomy, making the galaxies brighter than they would otherwise be, for example.

Nearer home, Sir Fred talked of the implications for the solar system, bearing in mind that the gravitational constant would have been 4/3 times its present value at the time of formation of the Earth–Moon system. The luminosity of the Sun would have been something like three times its present value (rather than less bright as used to be suspected) and the Earth would have been nearer the Sun than it is now because the effect of a decreasing value of G is to turn the planetary orbits into steadily expanding spirals. Sir Fred speculated on what the meteorological conditions might have been like at the time of formation of life on the Earth, possibly 3×10^9 years ago, and suggested that the gradual cooling of the terrestrial atmosphere and surface as G decreased and the Sun became less bright and further away might have been a factor controlling the type of life that could evolve.

Turning to geophysics, Sir Fred confessed to being happy with the kinematics but not the dynamics of continental drift. He suggested that a worldwide cracking of the surface to form the rigid plates, as the Earth expanded due to the changing value of G, might be a way out of the difficulty, and he speculated that similar processes may have to be taken into account on other planets, notably Jupiter.

NERVE

Receptors in Axons

from our Neurochemistry Correspondent

A REPORT by J. L. Denburg, M. E. Eldefrawi and R. D. O'Brien, of Cornell University, in a recent issue of the *Proceedings of the US National Academy of Sciences* (**69**, 177; 1972), which shows the presence, inside nerve axon membranes, of a macromolecule with many of the properties of the receptor for acetylcholine, promises to be of great interest, because it suggests that previous theories of axonal conduction may be incomplete.

Conduction of impulses along nerve fibres occurs by the propagation of brief electrical signals, termed "action potentials". According to the membrane concept, built up in the past thirty-five years, action potentials arise from a sudden change in the polarity of the cell membrane caused by a breakdown in its selective permeability to certain ions. A potential difference normally exists across the axon membrane, because its permeability to potassium and chloride ions is much greater than to sodium ions. Stimulation, however, causes the membrane to become leaky to sodium ions, and as a result a sudden influx of sodium ions occurs and the potential of the membrane is rapidly reversed. The phase of sodium entry is transitory, and is followed within 1 or 2 milliseconds by an outward movement of potassium ions, which tends to return the membrane potential to its initial level, and hence restore the original selective permeability of the membrane such that it is once more excitable. Because nerve fibres are to a certain extent like conducting cables, an impulse at a particular point spreads to adjacent parts of the fibre, and this in turn causes a regenerative entry of sodium ions, leading to a full-sized action potential. Thus impulses are propagated in an all-or-none fashion along the fibre.

By contrast, transmission of impulses across synapses, at the terminals of nerve fibres, is believed to occur by the release of certain chemical transmitters, which diffuse across the synaptic cleft and interact with specific receptors on the postsynaptic membrane. At the mammalian neuromuscular junction, interaction of the transmitter, acetylcholine, with receptors on the muscle surface causes an indiscriminate increase in cation permeability, thereby reducing the membrane potential to zero and triggering muscle action potentials.

Sensitivity to acetylcholine is normally restricted to junctional regions, but Nachmansohn has shown that impulses in nerve and muscle are blocked in the presence of large doses of inhibitors of cholinesterase, the enzyme which destroys acetylcholine. He has suggested that a local release of acetylcholine, similar to that occurring at nerve endings, is responsible for the excitation of axon membranes and its underlying permeability changes. Drugs such as curare, which is a competitive antagonist to acetylcholine at end-plate receptors, do not, however, affect axon conduction, and other drugs, such as tetrodotoxin and tetraethyl ammonium, which block axon conduction by specifically interfering with the sodium and potassium channels in nerve, have no effect on the sensitivity of end-plate receptors to applied acetylcholine, and this has led to severe criticism of Nachmansohn's theory.

The possibility that certain drugs act specifically at ACh receptors, together with a potentially good source of postsynaptic membranes rich in such receptors in the electric organs of certain fish, has stimulated a tremendous surge of interest recently in methods for the isolation and characterization of the cholinergic receptor. O'Brien and his colleagues have themselves used the technique of reversible equilibrium dialysis to study the binding of cholinergic drugs to a particulate fraction from the *Torpedo* electric organ, and in the present experiments they extend these methods to use on preparations of axon plasma membrane from lobster nerves.

Denburg *et al.* found that the membrane preparation bound labelled nicotine, a known cholinergic ligand, with a K_D of 0.42 μM, indicating a reasonable affinity. Even in the presence of a high concentration of a cholinesterase inhibitor, binding of ^{3}H-acetylcholine could not be detected, but acetylcholine inhibited the binding of nicotine with a K_i of 43 μM, suggesting a relatively low affinity. The binding of nicotine was also inhibited by several other drugs known to act as cholinergic receptors, including α-bungarotoxin, but was unaffected by non-cholinergic drugs. Furthermore, it was found that the local anaesthetic, procaine, which blocks axon conduction by interfering with both sodium and potassium channels in some way as yet unknown, also depressed nicotine binding.

The presence, in axon membranes, of a component capable of binding cholinergic agents suggests that Nachmansohn's theory needs to be reconsidered. It has, however, not been proved that binding of agonist to the "receptor" macromolecule is a necessary element in conduction—axons perfused with simple saline solutions are capable of conducting impulses for several hours. O'Brien and his colleagues quote evidence that curare, injected inside axons, blocks conduction, but this is only in concentrations of 1 to 10 mM. Similarly, the inhibition of nicotine binding by procaine observed in the present experiments is not sensitive to the concentration of calcium, as is the effect of procaine on conduction, which suggests that the two effects may be independent.

Preliminary indications are that the nicotine-binding site is a phospholipoprotein molecule. It is possible that large molecules of this sort are a necessary structural component of all membranes and, although they remain on the inside of the membrane at indifferent sites, at the highly specialized junctional sites to which sensitivity to acetylcholine is normally restricted, they are mobilized to the outside of the membrane.