of large populations of cells, rather than controlling individual targets on a one-to-one basis. Both Chan-Palay (*Cerebellar Dentate Nucleus* Springer-Verlag, 1977) and Descarries *et al.* (*op.* cit.) speculate that these aminergic systems may be used as neuromodulators, biasing the responses of target cells to classical neurotransmitters and shaping the activities of large neuronal regions.

Regardless of whether non-synaptic boutons turn out to release neurotransmitter, a neuromodulatory role for these diffuse aminergic projections is suggested, both by their anatomical arrangement and by neurophysiological data. Freedman and coworkers for example, recently reported that noradrenergic activation, although suppressing spontaneous firing of cerebellar Purkinje cells produced a relative enhancement of the Purkinje response to synaptic inputs from other cells (*Expl Neurol.* **55,** 269; 1977). Noradrenergic projections to the forebrain contrast with the fibre pathways of classic neuroanatomy not only in the diffuseness of their distribution, but also in topographic organisation. In classically described long pathways the terminal projections of individual cells are generally arranged so that a map of the total projection field corresponds topographically with the distribution of cell bodies. R. Y. Moore and coworkers have found that this sort of organisation does not occur in noradrenergic projections from the locus coeruleus to the neocortex; rather, projections from a single cell are widespread, with vast overlapping (*A. Rev. Neurosci.* in the press). Interestingly, many of the brain regions receiving noradrenergic input make reciprocal connections back to the tiny locus coeruleus nucleus. These observations suggest that the diffuse ascending aminergic systems represent a distinct category of neuronal organisation.

A neuromodulatory role is concordant with a massive literature implicating amines in various aspects of behaviour. A leading biochemical theory of schizophrenia suggests malfunction of dopaminergic systems. Alterations in mood are correlated with neuronal availability of noradrenaline. Many studies have linked catecholamines and indolamines to vigilance, reward, and learning, yet it has not been possible to identify a specific aminergic role in any of these behavioural processes. That elucidation may now be a step closer.

Egg activation

from Duncan O'Dell

WHEN an egg is fertilised, many of its properties change promptly. Most species show an increase in the rate of respiration, protein synthesis is turned on, permeability and transport characteristics of the surface membrane change, a block to the entry of supernumary sperm is established and meiosis, where appropriate, is resumed. It has long been considered that during oogenesis an egg acquires all the machinery necessary to respond rapidly to fertilisation, but that these several responses become 'blocked' until they are 'activated' by the entry of a sperm. For many years, there has been a search for the 'switch' or 'switches' that would serve to activate eggs and explain why so many different processes get turned on more or less together. This search was complicated by the fact that some eggs, such as those of sea urchins, can be parthenogenetically activated by any of a long and confusing list of treatments whereas others, such as those of sea squirts, are refractory to most procedures tried. Matters became much clearer in 1974 when Steinhardt and Epel (*Proc. natn. Acad. Sci. U.S.A.* **71,** 1915) showed that the ionophore for divalent cations, A23187, would activate echinoderm eggs; subsequent work by these and other authors has shown both that many other eggs can be similarly activated and that the movement of calcium ions is intimately involved in the process.

In a more recent analysis (Johnson *et al. Nature* **262,** 661; 1976) the activation of sea urchin eggs was divided into two stages. The first, which occurs in the minute after fertilisation or activation, involves the exocytosis of the granules under the surface of the egg leading to various surface changes and it is this event that can be brought about by the calcium ionophore. The second stage, about three or four minutes later, involves the onset of macromolecular syntheses and the most interesting feature here is that the first stage is not a prerequisite for the second. A number of treatments—ammonia, procaine, nicotine—all lead directly to the metabolic activation of the egg. Johnson *et al.* showed that all these agents caused an efflux of H^+ ions with a subsequent rise in the intracellular *p*H of the eggs. If this efflux of acid was blocked in various ways, the second stage of activation did not occur. It was then suggested that low intracellular *p*H served as the natural 'block' of metabolism before fertilisation, with the caveat that this sort of analysis has not yet been performed on many species of egg. Johnson *et al.* concluded by speculating that such shifts of intracellular *p*H could be regulating mechanisms elsewhere when quiescent cells resume division.

In this issue of *Nature* (page 590) Lopo and Vacquier take up the challenge presented by this speculation. First, the observation that intracellular *p*H rises after fertilisation is confirmed. But the changes in *p*H have also been followed for much longer during development, and it has been found that the higher *p*H of the newly fertilised egg is not maintained for long. Since the actively dividing cells of cleavage stage embryos seem to have an intracellular *p*H lower than that of the 'blocked' mature egg cell, it would seem that low *p*H alone is no absolute barrier to the processes involved in preparing for mitosis. The initial rise in *p*H, then somehow serves irreversibly to 'unblock' the egg. However there may still be a link between DNA synthesis and gross intracellular *p*H as Lopo and Vacquier show by use of procaine. This drug promotes DNA synthesis and a high intracellular *p*H; when procaine is removed, both fall.

It seems established, then, that at least in sea urchin eggs an early event following fertilisation is a rise in intracellular *p*H and that this rise is associated with the onset of the processes of early development, but the higher *p*H is not necessary for the completion of these processes. Clearly, there is scope for further analysis here. All these *p*H measurements were made on egg homogenates and subtle local variations within the cell would have been missed. The mode of action of a drug such as procaine is by no means exactly certain. More work needs to be done before one can interpret the consequences of a rise in intracellular *p*H with confidence. However, the past three years, starting with Steinhardt and Epel's experiments on A23187, have taught us a great deal about fertilisation and egg activation. Although the definitive analysis is not yet quite in sight important experiments are being done and there is a feeling that an interpretation will be made. At the beginning of this century good scientists worked hard on the problem but mainly produced a baffling list of egg activating treatments, there is now hope that the scientific great-grandchildren of pioneers like J. Loeb will be able to interpret that list in terms of calcium levels, *p*H shifts, surface membrane changes and so on. □

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