

## EDITORIAL

### Pursuing the actions of psychotropic drugs: receptor sites and endogenous cerebral programmes<sup>1</sup>

In discussing the logic of screening newly synthesized compounds as drugs, Creese (1978) writes: 'for example, the exact relationship between the mechanism by which a drug relieves a schizophrenic of auditory hallucinations and stops a rat from jumping up on a pole to avoid an electric shock (a common screen for antischizophrenic agents) is hard to discern'. It is, however, an important matter to pursue, for chemotherapeutic experience has shown (McIlwain, 1957) that success in finding drugs of value has followed the effective biological analysis of a system, rather than coming from less specifically oriented syntheses. Creese's (1978) account takes the hunt to extracellular receptor-binding sites as a means of providing biochemical points of action for psychotropic drugs in electrophysiological, pharmacological and behavioural studies. Correlations are shown between inhibition of stereotyped movements in the rat, and of neuroleptic binding to membrane preparations from the striatum; and between the binding and clinically effective doses of the drugs. These findings deepen the impression of a real connection between schizophrenic symptoms and the quoted aspects of animal behaviour, without indicating how this comes about.

#### EXTRACELLULAR NEUROTRANSMITTER-RECEPTORS

Further clues have, however, been given by the nature of the compounds with which neuroleptics interact at their receptors for, in several cases, these endogenous ligands are the catecholamines dopamine and noradrenaline. We thus arrive at a group of ideas on psychoses which implicate biogenic amines and receive support, for example, from the schizophrenia-like effects induced by amphetamines. As is noted by Matthyse (1975), these ideas have led to a number of catecholamine theories of the aetiology of schizophrenia whereby the illness might result from release of too much dopamine at central synapses; or the dopamine-receptors there might be hypersensitive; or systems which dopamine operates, or which are modulated by dopamine, might be defective. Following some discrepant data the latter ideas have been developed further to multi-transmitter and receptor theories, whereby a balance between catecholamine and acetylcholine or metabolites (Davis, 1975), or between catecholamines and endorphins (Volavka *et al.* 1979), was the factor disturbed in the illness: that is, the abnormality lay in one or more extracellular neurotransmitter-receptors, in ER, or in ER<sub>1</sub> plus ER<sub>2</sub>...ER<sub>n</sub>.

Additional hypotheses are still, however, needed to understand the particular symptom-pattern in schizophrenia, or the particular animal behaviour with which it is compared in the quotation (Creese, 1978) which begins this account. Thus, it must be supposed that the excess dopamine or the hypersensitive receptors occur at regions causing auditory hallucinations in man or at those facilitating or prompting pole-jumping in shocked rats: which is akin to rewriting the initial problem. This problem should, however, be broadened, for other sensory abnormalities which occur in schizophrenia are relieved by neuroleptics: for instance, abnormalities of sensory thresholds (Ungerstedt & Ljungberg, 1974); and other aspects of animal behaviour are affected by the drugs: for example, avoidance reactions in shuttle-box experiments (Andén, 1974). It is the relationship between endogenous components of animal behaviour and of perception which is hard to discern.

<sup>1</sup> Address for correspondence: Professor Henry McIlwain, Department of Biochemistry, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF.

## EXTRACELLULAR RECEPTOR LOCATION

Experiments which localize neurotransmitter-receptors give some further enlightenment here. Animals in which localized damage was caused to dopamine neurons by stereotaxic injections of 6-hydroxydopamine showed no immediate motor disability, but lacked orienting reactions to visual, tactile and odour stimuli (Ungerstedt & Ljungberg, 1974). Deficits were shown also in more complex tasks, including maze-running for reward, and these deficits were restored by administering either the dopamine-precursor dihydroxyphenylalanine, or apomorphine which stimulated the relevant receptors.

These experiments attractively display how essential are the neurotransmitters and neurotransmitter-receptors to animal behaviour: as indispensable links between input stimuli and a complex behavioural output. The initial quotation (Creese, 1978), however, asks more: it seeks to discern mechanisms between two groups of observations concerning chemical substances and behaviour, and 'although behavioural biologists have long sought to decipher the chemical coding of behaviour the search for these codons has been elusive' (Reis, 1974). To judge by the experiments just discussed, the codons are not simply chemicals, but chemicals in particular cytological locations in cells carrying particular receptors and, understandably, much other metabolic machinery.

## RECEPTOR-CONTROLLED PRODUCTS

Current investigation of neurotransmitter-receptors has led to extensive development of techniques for their measurement (Yamamura *et al.* 1978; O'Brien, 1979) and, indeed, to a feeling that here was a 'non-catalytic biochemistry' of cellular response. It is therefore to be emphasized that modification of enzyme catalysis is a major target of receptor control and that this applies *par excellence* to catecholamine receptors. Major products controlled by catecholamine receptors are cyclic nucleotides which very much have a life of their own in the brain (McIlwain, 1972; Newman & McIlwain, 1977). In particular, the nucleotides cyclic AMP and cyclic GMP when generated postsynaptically catalyse further changes which alter neuronal membrane potentials and increase or decrease cell-firing tendency.

Preconceptions about how the cyclic nucleotides acted caused some authors to write as though action of the nucleotides was extremely brief, and localized to immediately adjacent molecules at the cell-membrane point which received the neurotransmitter; but observations throughout have emphasized the limitations of such presuppositions. Concentrations of the nucleotides in the brain are altered by excitation and by neurotransmitters, and the nucleotides may persist in altered concentrations for some minutes after the perturbing stimuli have terminated (Newman & McIlwain, 1978). As one role of the cyclic nucleotides is as neurotransmitter-mediators, these observations are relevant to the modulation of cell-firing observed after cerebral stimulation, or after application of neurotransmitters: that is, the modification of cell-firing or firing tendency can be expected to persist for periods of up to some minutes after momentary transmitter-release. This is entirely parallel to the role of the same nucleotides in other cells or organs, when the responses which they mediate, e.g. glycogenolysis or lipid mobilization, may also last some minutes. Compared with most other mammalian organs, the brain is unusually rich in cyclic nucleotides and active in their metabolism, so that it may be judged that the nucleotides subserve functions which are highly developed in the brain.

Clues to the nature of such functioning have come by considering the role of the cyclic nucleotides in other cells and organs. Here they are 'second-messengers' which continue intracellularly the signal-transmission initiated at a cell-exterior by 'first-messengers' which are extracellularly acting humoral agents: for example, an agent acting at fat cells or muscle is also a catecholamine – adrenaline. Catecholamine-receptors here represent one set of transducers between humoral signal and cellular responses. But these responses do not necessarily occur at the points at which the cyclic nucleotides are generated; much occurs at lipid vesicles and glycogen granules, intracellular entities separated by (in cellular dimensions) appreciable distances from the extracellularly membrane-sited catecholamine receptors. The realm of the first-messenger humoral agents – hormone or neurotransmitter – is in these instances extracellular; that of the nucleotide second-messengers and their second-messenger

receptors are intracellular. The nucleotide function especially developed in the brain may thus concern second-messenger transmission among different regions of its unusually elongated nerve cells.

### INTRACELLULAR SECOND-MESSENGER RECEPTORS AND MOVEMENTS

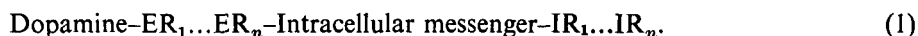
Second-messengers also act at receptor-sites, distinct from those of first-messengers but again susceptible to chemical characterization and cellular localization. On seeking cyclic-nucleotide combining entities in various fractions of cerebral tissues, it was found that intracellular receptors occurred at neuronal membrane sites, including postsynaptic sites, and also cytoplasmically (Walter *et al.* 1978; McIlwain, 1978, 1980; Newman *et al.* 1980). The best-established points of cyclic nucleotide generation are at the postsynaptic region of synaptic junctional complexes. Translocation of nucleotide is thus involved within a given junction and between junctions; and also between junctions and cytoplasmic regions and other organelles accessible from the cytoplasm.

Intracellular movements in the brain are highly organized: some 10% of the soluble protein of the brain is tubulin, much of which *in situ* is organized as longitudinal tubules in the axons and dendrites of constituent cells and which has there a function in the intracellular transport of substances and particles. Cyclic nucleotides and their precursors, and neurotransmitters and their precursors, in some cases vesiculated, are among the entities transported (see Newman & McIlwain, 1978). Note, however, that the cytoplasmic movement of neurotransmitters, or of first-messengers generally, is of very different status from the cytoplasmic movement of the cyclic nucleotides as second-messengers. Neurotransmitters have been observed moving towards nerve-terminals where later they may be released and only after their release may act. Nucleotides have been observed moving along axons and dendrites and are then already in the cytoplasmic regions which are their sphere of action. Thus, when the nucleotides undergo cytoplasmic transport, they are enabled to act successively at a number of intracellular receptor sites,  $IR_1 \dots IR_n$ , along their route of movement and during their life-time of some minutes.

The long dendritic branches of large cerebral neurons are especially significant regions in considering the movements of cyclic nucleotides (McIlwain, 1976, 1979). They carry many hundreds of terminals; a given neuron often makes multiple synapses with a given dendritic branch. Second-messenger nucleotide generated postsynaptically at axosomatic or at dendritic junctions may proceed along the dendrite and activate such of the successive postsynaptic or other regions as are sensitive to it: that is, those which carry the appropriate second-messenger receptors. Details of the activation, and consideration of other components of cyclic nucleotide systems which also undergo cytoplasmic movements, have been given elsewhere (McIlwain, 1977, 1978).

### INTRACELLULAR RECEPTORS AND ENDOGENOUS CEREBRAL PROGRAMMES

An outcome of the movement of cyclic nucleotides intracellularly along dendritic receptor-arrays is thus a temporal modulation of cell-firing or firing tendency, which corresponds to the spatial pattern of nucleotide-sensitive regions,  $IR_1 \dots IR_n$ , along the dendrite. Supporting evidence has been quoted (McIlwain, 1977) from observation of prolonged effects on cell-firing rates in eight separately studied cerebral systems, including instances of concomitant changes in cyclic nucleotide content and firing rate following the stimulation of noradrenergic innervation. The action of dopamine on cerebellar Purkinje cells and on caudate nucleus cells was to alter their pattern of firing (Bloom, 1975, 1978), actions also given by cyclic nucleotides. Responses to dopamine, but not to cyclic AMP, were antagonized by several antipsychotic phenothiazines, including chlorpromazine and fluphenazine. These drugs thus act as components ER in the sequence (1):



Sequence (1) involves several other reactants, detailed elsewhere (McIlwain, 1977); its components  $IR_1 \dots IR_n$  are considered to condition the normal firing pattern of the neuron concerned and to be formed or positioned during development while the organism involved is receiving sensory input,

environmental and proprioceptive. That noradrenergic innervation of the cerebral cortex which has been found necessary to programmed performance in rats (Anlezark *et al.* 1973) can be interpreted in terms of its providing intracellular messenger which 'reads' the component  $IR_1 \dots IR_n$ . Such components, comprising series of nucleotide-sensitive receptors in the many available dendritic branches, offer mechanisms both for endogenous motor programmes and also for constructing the internal model of environmental events that is believed to be necessary to perception and memory.

The mechanisms sought by Creese (1978) in the initial quotation of this account involve the material bases for programmed series of endogenous cerebral activities, as manifested by signs and symptoms of hallucinations in man and by behavioural responses in animals. Activation of components  $IR_1 \dots IR_n$  of sequence (1), which conceptually links these phenomena, has been noted above to have consequences detectable electrophysiologically, and the emitted cerebral events of Weinberg *et al.* (1974) may also represent such an output. In certain schizophrenics hallucinatory activity was reported to be correlated with a particular pattern seen electrically in the septum (Bloom, 1978). Study of intracellular and extracellular receptor-sites, of receptor-controlled products and of their translocation can now offer vantage-points for discernment of behavioural mechanisms and of potential therapeutic approaches. Receptors, so prominent in the theoretical writing of Paul Ehrlich around 1900, did not feature much in his selection or synthesis of drugs (see McIlwain, 1957); as indicated above, however, chemotherapists now have the advantage of extensively developed techniques for measurement of receptor sites, and increasing attention could well be given to applying such measurements to the later stages of sequence (1).

HENRY MCILWAIN

## REFERENCES

- Andén, N. E. (1974). Antipsychotic drugs and catecholamine synapses. *Journal of Psychiatric Research* **11**, 97–104.
- Anlezark, G. M., Crow, T. J. & Greenaway, A. P. (1973). Evidence that noradrenergic innervation of the cerebral cortex is necessary to learning. *Journal of Physiology* **231**, 119–120.
- Bloom, F. E. (1975). The role of cyclic nucleotides in synaptic function. *Review of Physiology, Biochemistry and Pharmacology* **74**, 1–103.
- Bloom, F. E. (1978). Modern concepts in electrophysiology for psychiatry. In *Biochemistry of Mental Disorders* (ed. E. Usdin and A. J. Mandell), pp. 31–52. Dekker: New York.
- Creese, I. (1978). Receptor-binding as a primary drug screening device. In *Neurotransmitter Receptor Binding* (ed. H. I. Yamamura), pp. 141–170. Raven: New York.
- Davis, J. M. (1975). Critique of single-amine theories. *Research in Nervous and Mental Disease* **54**, 333–346.
- McIlwain, H. (1957). *Chemotherapy and the Central Nervous System*. Churchill: London.
- McIlwain, H. (1972). Regulatory significance of the release and action of adenine derivatives in cerebral systems. *Biochemistry Society Symposium* **36**, 69–85.
- McIlwain, H. (1976). An extended messenger-role in the brain for cyclic AMP. *FEBS Letters* **64**, 271–273.
- McIlwain, H. (1977). Extended roles in the brain for second-messenger systems. *Neuroscience* **2**, 357–372.
- McIlwain, H. (1978). Synaptic mediators and the structuring of cerebral activity. *Progress in Neurobiology* **11**, 189–203.
- McIlwain, H. (1979). Intracellular synaptic mediators and the endogenous simulation of neural input to the brain. In *Brain Mechanisms in Memory and Learning* (ed. M. A. B. Brazier), pp. 71–79. Raven: New York.
- McIlwain, H. (1980). Brain: intracellular and extracellular purinergic receptor-systems. In *Purinergic Receptors* (ed. G. Burnstock). Chapman & Hall: London (in the press).
- Matthysse, S. W. (1975). Epilogue. In *Catecholamines and Schizophrenia* (ed. S. W. Matthysse and S. S. Kety), pp. xv–xviii. Pergamon: Oxford.
- Newman, M. & McIlwain, H. (1977). Adenosine as a constituent of the brain and of isolated cerebral tissues, and its relationship to the generation of adenosine 3'5'-cyclic monophosphate. *Biochemical Journal* **164**, 131–137.
- Newman, M. & McIlwain, H. (1978). Cellular site and state of combination of adenosine 3'5'-cyclic monophosphate persisting after excitation of cerebral tissues. *Biochemical Journal* **170**, 73–79.
- Newman, M. E., Patel, J. & McIlwain, H. (1980). Protein-bound cyclic AMP and histone kinase activities in cerebral cortical preparations. Submitted for publication.
- O'Brien, R. D. (1979). *The Receptors: a Comprehensive Treatise. I. General Principles and Procedures*. Plenum: New York.
- Reis, D. J. (1974). Consideration of some problems encountered in relating specific neurotransmitters to specific behaviours or disease. *Journal of Psychiatric Research* **11**, 145–148.
- Ungerstedt, U. & Ljungberg, T. (1974). Central dopamine neurons and sensory processing. *Journal of Psychiatric Research* **11**, 149–150.
- Volavka, J., Davis, L. G. & Ehrlich, Y. H. (1979). Endorphins, dopamine and schizophrenia. *Schizophrenia Bulletin* **5**, 227–239.
- Walter, V., Kanof, P., Schulman, H. & Greengard, P. (1978). Adenosine 3'5'-monophosphate receptor proteins in mammalian brain. *Journal of Biological Chemistry* **253**, 6275–6280.
- Weinberg, H., Grey Walter, W., Cooper, R. & Aldridge, V. J. (1974). Emitted cerebral events. *EEG and Clinical Neurophysiology* **36**, 449–456.
- Yamamura, H. I., Enna, S. J. & Kuhar, M. J. (1978). *Neurotransmitter Receptor Binding*. Raven: New York.