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REVIEW ARTICLE

The structure and mechanism of neurotransmitter receptors

Implications for the structure and function of the central nervous system

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INTRODUCTION

Recently certain generalities concerning the structure and mechanism of action of cell surface receptors, particularly those for neurotransmitters, have become apparent. In this article I discuss these generalizations and consider their implications for receptor function and also for the structure and function of the central nervous system in general. The literature up to June 1987 is covered.

THE STRUCTURE AND MECHANISM OF ACTION OF RECEPTORS

In the last few years a number of receptor proteins have been isolated and characterized to a greater or lesser degree and in many cases their mechanisms of action have been clarified. It is becoming apparent that structure and mechanism are interdependent, and two broad classes of receptor may be discerned largely according to the speed of the response mediated (McGeer *et al.*, 1978; Strange, 1983).

Fast responding (class I) receptors

One class of receptor, which I shall term class I for brevity, when activated by binding neurotransmitter, mediates very rapid (milliseconds) alterations in the distribution of ions across the relevant membrane. The best and most characterized example here is the nicotinic acetylcholine receptor which binds acetylcholine and mediates the passage of sodium and potassium ions across membranes bearing the receptor (Barnard & Dolly, 1982; Conti-Tronconi & Raftery, 1982; Noda *et al.*, 1982, 1983*a*,*b*). Other examples of class I receptors are given in Table 1. Class I receptors are linked directly to an ion channel (Fig. 1) and there is no evidence for the involvement of guanine nucleotide regulatory proteins or second messengers. What we know about the structure of class I receptors (Table 1) suggests that each consists of an oligomeric transmembrane protein containing both the agonist-binding site or sites and the ion channel. The molecular mass of the oligomer is 200–250 kDa and it is composed of subunits of about 50 kDa which may be a common structural feature. Recent gene cloning studies on the glycine receptor (Grenningloh *et al.*, 1987) and $GABA_A$ receptor (Schofield *et al.*, 1987) emphasize this point. The predicted structures of the subunits of these receptors show homology with those of the nicotinic acetylcholine receptor. Each contains four putative membrane-spanning segments, so that these receptors and perhaps class I receptors generally may be members of a superfamily of homologous proteins based on

Table 1. Class I receptors: structure and function

Under subunit composition, values are given for the molecular sizes of subunits derived from electrophoretic analysis except for glutamate where values are from target size analysis. Values derived from the amino acid composition given by gene cloning are given in parentheses.

Receptor subtype	Function	Overall molecular size (kDa)	Subunit composition (kDa)	References
Cholinergic (nicotinic)	Excitatory	250	α, 40 (50); β, 50 (54); γ, 60 (56); δ, 65 (58); $\alpha_2\beta\gamma\delta$	Barnard & Dolly (1982), Conti-Tronconi & Raftery (1982), Noda *et al.* (1982, 1983*a*,*b*)
$GABA_A$	Inhibitory	230	α, 53 (49); β, 57 (51)	Stephenson (1985), Schofield *et al.* (1987)
Glutamate	Excitatory	263 209 (NMDA) 77 (kainate) 52 (quisqualate)		Bardsley & Roberts (1985), Honore *et al.* (1987)
Glycine	Inhibitory	246	48 (48), 58	Pfeiffer *et al.* (1982), Grenningloh *et al.* (1987)

Abbreviations used: GABA, γ-aminobutyric acid; 5HT, 5-hydroxytryptamine (serotonin); LHRH, luteinizing hormone releasing hormone; NMDA, *N*-methyl-D-aspartic acid.

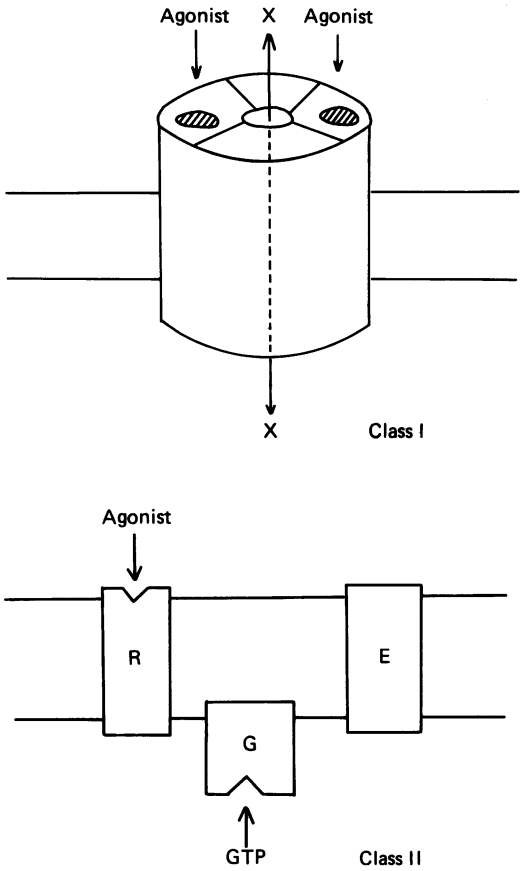

Fig. 1. Organization of class I and class II receptors

A class I receptor is shown as a transmembrane oligomeric protein containing ligand-binding subunits and a central ion channel specific for X (Na^+/K^+ for nicotinic acetylcholine and glutamate receptors, Cl^- for $GABA_A$ and glycine receptors). The nicotinic acetylcholine receptor contains five subunits, two of which contain agonist-binding sites, whereas the $GABA_A$ receptor contains four subunits, two of which are likely to contain agonist binding sites. A class II receptor (R) is shown together with a G protein (G) and effector (E) (adenylate cyclase, phospholipase C or ion channel). The interactions between the different components and the convergence of signals from different receptors on a single effector are discussed in the text.

related genes. Depending on the selectivity of the ion channel contained in the oligomer, activation of the receptor by the neurotransmitter can generate a rapid depolarizing (excitatory) or hyperpolarizing (inhibitory) signal.

Slow responding (class II) receptors

A much more diverse group of neurotransmitters (e.g. monoamines) and neuromodulators (e.g. neuropeptides) act at receptors (class II) which show slower responses (seconds) and are analogous to the actions of hormones at cell surface receptors. The class II receptors, where isolated (Table 2), have a more simple structure than class I receptors, consisting of a single polypeptide containing the receptor site. The simplicity is more apparent than real, however, as the receptor is only a part of the transmembrane signalling apparatus for class II receptors (Fig. 1). In addition to the receptor there is also a guanine nucleotide regulatory protein (G-protein) (Bourne, 1986) acting as a transducer to an appropriate effector system, the whole apparatus being in the membrane or associated with it. The effector systems that are well characterized in the central nervous system are the enzymes adenylate cyclase (Gilman, 1984) or the phosphatidylinositol bisphosphate specific phospholipase C (referred to subsequently as phospholipase C) (Berridge & Irvine, 1984).

It has recently been reported that receptors in the periphery and central nervous system can couple via G-proteins directly to ion channels e.g. muscarinic acetylcholine receptors, $GABA_B$ receptors, adenosine receptors and serotonin ($5HT_{1A}$) receptors to K^+ channels (Breitweiser & Szabo, 1985; Andrade *et al.*, 1986; Kurachi *et al.*, 1986; Pfaffinger *et al.*, 1986), $GABA_B$ receptors, somatostatin receptors and opiate receptors to Ca^{2+} channels (Holz *et al.*, 1986; Lewis *et al.*, 1986; Scott & Dolphin, 1986; Hescheler *et al.*, 1987). These systems provide further classes of receptor–G-protein–effector array. Preliminary evidence for receptor–G-protein linkage to phospholipase A_2 has also been presented in thyroid cells (Burch *et al.*, 1986) and MDCK cells (Slivka & Insel, 1987) so that this mechanism could also be found eventually in the central nervous system. There are several kinds of G-protein which may be related to the effector systems and the organization of the systems will be considered below.

The effector systems adenylate cyclase and phospholipase C, when activated, generate alterations in second messengers (cyclic AMP, inositol trisphosphate, diacylglycerol) each of which can ultimately lead to alterations in the activity of protein kinases (Nestler & Greengard, 1983). The phosphorylation state of target proteins can thus be altered and it can be seen that the neurotransmitter or neuromodulator serves to provide this change in protein phosphorylation, the enzymic nature of the signal providing for amplification of the signal. The nature of the phosphorylation targets is beginning to be understood and some examples are adenylate cyclase (Yoshima *et al.*, 1986), receptors (Benovic *et al.*, 1985; Huganir *et al.*, 1986), ion channels (Hescheler *et al.*, 1986; Higashida & Brown, 1987) and proteins of as yet uncertain function (Nestler & Greengard, 1983); it should be clear that such an enzyme-based system must be slow in responding.

Where a class II receptor couples via a G-protein to an ion channel without the intervention of a second messenger and protein kinase the non-enzymic nature of the signalling system might be expected to be somewhat quicker than the enzymic. However, the muscarinic receptor-linked K^+ channel shows a latency of 100 ms (Hartzell, 1981; Sakmann *et al.*, 1983; Soejima & Noma, 1984), indicating that the intervention of a G-protein slows the system down significantly compared with a class I receptor.

Thus class II systems are generally slow in responding and will be associated with slower modulatory effects in neurones, e.g. alteration of transmitter release, alteration of neuronal excitability, receptor internalization. Such slower changes may be relevant to the laying down of information for memory storage (see, for example, Goelet *et al.*, 1986).

Table 2. Class II receptors: structure and function

Effectors: AC, adenylate cyclase; PIP_2-PLC, phosphatidylinositol bisphosphate-specific phospholipase C; KC, potassium channel. Under subunit size values are given for molecular size derived by electrophoretic analysis. Values in parentheses are from the amino acid composition derived by gene cloning; a further value of 46 kDa for human β-adrenergic receptors of undefined β subclass was reported by Chung *et al.* (1987).

Receptor	Subtype	Effector	Subunit size	References
Adrenergic	α_1	PIP_2-PLC↑	59, 80	Graham *et al.* (1982) Lomasney *et al.* (1986)
	α_2	AC↓	64	Regan *et al.* (1986)
	β_1	AC↑	40–45 (54) (red cell); 65–67 (other)	Moxham *et al.* (1986), Yarden *et al.* (1986)
	β_2	AC↑	58–60 (red cell); 65–67 (46) (other)	Dixon *et al.* (1986), Moxham *et al.* (1986), Kobilka *et al.* (1987)
Cholinergic (muscarinic)	M_1/M_2	PIP_2-PLC↑; AC↓; KC↑	70–80 (51, M_1, M_2)	Berrie *et al.* (1985), Peterson *et al.* (1985), Kubo *et al.* (1986*a*,*b*), Peralta *et al.* (1987)
Dopaminergic	D_1	AC↑	72	Amlaiky *et al.* (1986)
	D_2	AC↓; PIP_2-PLC↓	83–94	Amlaiky & Caron (1985), Lew *et al.* (1985), Redouane *et al.* (1985), Niznik *et al.* (1986), Worrall *et al.* (1986)
Opiate	δ	AC↓	53–58	Howard *et al.* (1985), Simonds *et al.* (1985)
	μ	AC↓	58–65	Gioannini *et al.* (1985), Howard *et al.* (1985), Newman & Barnard (1984), Cho *et al.* (1986)
Serotonergic	$5HT_2$	PIP_2-PLC	67	Wouters *et al.* (1987)

ORGANIZATION OF CLASS II SYSTEMS

The existence of three groups of components (receptor/G-protein/effector) in class II systems offers scope for considerable complexity and it is useful to consider whether any general organizational principles can be discerned.

G-protein level

There are several kinds of G-protein and these form a family of heterotrimeric proteins with different α-subunits but common $\beta\gamma$ subunits (Gilman, 1984; Chabre, 1987). G_s (α 45 kDa), G_i (α 41 kDa) and G_o (α 39 kDa) have been well defined (Gilman, 1984; Sternweis & Robishaw, 1984; Katada *et al.*, 1986) and several reports exist of further G proteins with α subunits of 40 kDa (Michel *et al.*, 1986; Milligan *et al.*, 1986; Katada *et al.*, 1987). G_s is sensitive to cholera toxin, whereas effects mediated via G_i, G_o and G(α40) are sensitive to pertussis toxin. In addition a role for the *ras* proto-oncogene products as G-coupling proteins has been proposed (Chiarugi *et al.*, 1986; Wakelam *et al.*, 1986).

Effector level

The effector systems are only beginning to be characterized at the biochemical level, but there is no strong evidence for subgroups of the effectors. Thus there is likely to be a single pool of adenylate cyclase in a cell whose activity is altered by different G-proteins. There are separate classes of G-protein (G_s and G_i) for receptors that stimulate and inhibit adenylate cyclase respectively, and signals from stimulatory and inhibitory receptors are integrated at the level of adenylate cyclase. It is not clear whether this is via opposing effects of G_s and G_i (Birnbaumer, 1987) or whether an indirect interaction occurs (Cerione *et al.*, 1986).

It would not be unreasonable to suppose that similar interactions take place at phospholipase C, although the system is poorly understood at present. The G-protein coupling receptors to phospholipase C is not G_s, and in some systems effects on phospholipase C are sensitive to pertussis toxin, implicating G_i, G_o or a similar protein, e.g. G(α40) (Michell & Kirk, 1986; Falloon *et al.*, 1986; Worley *et al.*, 1986). Many systems do not show sensitivity to pertussis toxin and the *ras* proto-oncogene products are being considered as alternative coupling proteins (Chiarugi *et al.*, 1986; Wakelam *et al.*, 1986) for phospholipase C-linked receptors.

Most receptors associated with phospholipase C elicit stimulation of the enzyme, although there are two systems where inhibition has been described in the nervous system [D_2 dopamine receptors (Simmonds & Strange, 1985) and NMDA glutamate receptors (Baudry *et al.*, 1986)]. It is not clear whether these are direct inhibitory effects, but if they are one might expect separate G-proteins to be associated with stimulatory and inhibitory systems.

Similarly where G-proteins are found to couple directly to ion channels then further subclasses may be evident. The linkage of muscarinic receptors to K^+ channels is sensitive to pertussis toxin, implicating G_i, G_o or a similar protein (Martin *et al.*, 1985), and evidence has

been presented for a potent action of a G protein with an α subunit of 40 kDa (Yatani *et al.*, 1987). In the case of Ca^{2+} channels a role for G_o has been suggested (Hescheler *et al.*, 1987). It should be remembered that these data were obtained from reconstitution experiments, which do not necessarily show that the G protein applied is the G protein that is physiologically relevant.

Receptor level

At the receptor level it is not clear whether one receptor can interact with separate G-proteins to influence more than one effector system or whether for each effector system (and thus each G-protein) a separate receptor species exists. Such receptor species might not necessarily be pharmacologically distinct but might differ only at the G-protein recognition sites. Some guidance on this can be obtained from examining the adrenergic receptor system. β_1 and β_2 adrenoceptors both couple via G_s to stimulate adenylate cyclase (Lefkowitz *et al.*, 1976), whereas α_1 adrenoreceptors couple via a G-protein to phospholipase C (Brown *et al.*, 1984; see also Johnson & Minneman, 1986) and α_2 adrenoceptors couple via G_i to inhibit adenylate cyclase (Exton, 1982).

If these principles are generalized then we might expect to find separate pharmacologically distinct receptor subtypes (and a separate G-protein) associated with each effector response for other receptors. Thus for muscarinic acetylcholine receptors which inhibit adenylate cyclase, stimulate phospholipase C and activate K^+ channels, it would be predicted that separate receptor subtypes might be linked to each effector response. Preliminary evidence from gene cloning studies suggests heterogeneity of muscarinic receptors in brain (Hulme & Birdsall, 1986; Kubo *et al.*, 1986*a*,*b*; Fukuda *et al.*, 1987; Peralta, 1987). It has been suggested that M_1 and M_2 subtypes exist as defined by their affinities for pirenzepine, but although there are suggestions of separate receptor-based responses (McKinney & Richelson, 1986; Fukuda *et al.*, 1987), definitive linkage of M_1 and M_2 receptors to different effector responses has not been established. Similarly D_2 dopamine receptors inhibit adenylate cyclase (Cooper *et al.*, 1986) and may inhibit phospholipase C (Simmonds & Strange, 1985) and distinct receptor subtypes may be found here too. It should, however, be emphasized that the class II receptors may contain considerable structural homologies. The predicted structures so far available from gene cloning studies suggest a common overall composition based on seven transmembrane helices with considerable homologies (Dohlman *et al.*, 1987). Thus class II receptors may form a second superfamily of proteins based on related genes. It would be predicted that the ligand-binding site would be a distinct entity in each receptor, but that the site for G-protein recognition might be very similar between receptors that interact with the same G-protein.

To conclude this section it may be instructive to consider the analogy of bacterial chemotaxis, where bacteria, via receptors, are able to perform taxis towards a range of attractants and away from a range of repellents. Some degree of convergence in signalling occurs whereby signals from separate receptors or agonists are integrated at a common transducer (Strange & Koshland, 1976). It seems that similar principles hold in the more complex systems described above but the convergence of signals from different receptors does not occur until after the G-protein, i.e. at the effector level.

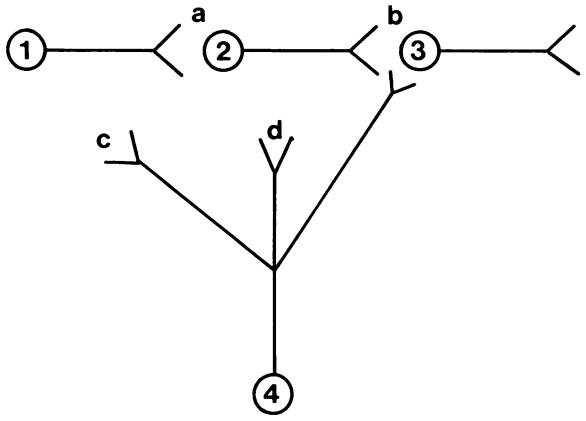

Fig. 2. Fast and slow circuits in the nervous system

A fast point-to-point signalling pathway is shown using neurones 1, 2 and 3 with either inhibitory or excitatory effects dependent on which class I receptor is present at synapse a on cell 2 and synapse b on cell 3. The pathway is modulated by branching neurone 4 which forms a synapse with class II receptors on to cell 3 but influences cells 1 and 2 diffusely via terminals c and d dependent on the positioning of class II receptors on neurones 1 and 2.

THE STRUCTURE OF THE CENTRAL NERVOUS SYSTEM

What implications do these generalizations have for the way the central nervous system is constructed and functions? Much of the way we think about the central nervous system is influenced by the rather detailed knowledge available on the neuromuscular junction (Kuffler *et al.*, 1984). This is, however, a system based on class I receptors and may not be a good guide to central nervous system function where class II receptors are very important as well. The neuromuscular junction consists of closely related pre- and post-synaptic membranes, and the system is designed for rapid responses typical of class I receptors. It is not unreasonable to suppose that class I systems in the central nervous system may be related functionally and to some extent structurally to the neuromuscular junction. Slower class II systems may not require this kind of organization and may therefore function in an entirely different manner.

Iversen (1984) and Schmitt (1984) have recently put forward ideas based on earlier suggestions of Horridge (1961) regarding the function of the central nervous system that correspond well with the generalizations about receptors made earlier. They have suggested that the central nervous system depends on two types of circuitry (Fig. 2). Rapid transfer of information occurs at synapses dependent on neurotransmitters acting via the fast class I receptors. It seems likely that these circuits are dependent on synapses with a close pre- and post-synaptic relationship to permit rapid transfer of information. The repertoire of transmitters acting in this way is limited as the number of class I receptors is small; the main excitatory signal may be glutamate although acetylcholine may also be important, and the main inhibitory signal may be GABA although glycine can act in this role in certain systems.

We can then envisage a major neuronal network in the central nervous system with fast point-to-point informa-

tion transfer based on glutamatergic and GABAergic synapses using class I receptors. This neuronal network is then modulated by separate neurones releasing neurotransmitters and neuromodulators acting at class II receptors. These substances alter the function of the class I receptor-based system and this will be a slower modulatory process. Although such systems seem frequently to operate at synapses there may be no need for a close pre- and post-synaptic relationship (see below). It may be sufficient for the modulatory substance to be released in such a way that it can diffuse and reach the appropriate receptor. If these ideas are generally correct, the parallels between receptor structure on the one hand, the neuronal systems on the other, have extra relevance.

These considerations may explain the limited variety of class I receptors. The function of the fast acting information transfer systems is determined by the detailed anatomical arrangements of the neuronal circuitry – the neurotransmitters act as true transmitters at clearly defined synapses. This has been termed an 'anatomically addressed' system by Horridge (1961). For the class II system the neurotransmitter or neuromodulator, once released, will act more slowly because of the post-receptor mechanism. It may also act more diffusely, influencing a number of sites rather than its site of action being determined by detailed neuroanatomical considerations as in class I systems. In this case specificity of action is determined by the specific interaction of a substance with its receptors (this interaction also generates a signal amplification) and the complexity of the nervous system is satisfied by having numerous receptors and hence modulators. Horridge termed these 'chemically addressed' systems. Whatever the synaptic specialization, class II receptor based systems must act more slowly owing to their underlying mechanistic constraints.

What support is there for these considerations from neuroanatomical and physiological observations?

Glutamate

Rapid (millisecond) excitatory actions of glutamate have been described, consistent with an action at a class I receptor (Watkins & Evans, 1981; Fagg & Foster, 1983; Fagg *et al.*, 1986; Macdermot & Dale, 1987). As befits glutamate for its role as a major excitatory transmitter, it is implicated as transmitter in many pathways in the central nervous system and some evidence for close synaptic interactions has been presented (Cotman *et al.*, 1987). Glutamate receptors are only beginning to be classified (Fagg & Foster, 1983; Fagg *et al.*, 1986; Cotman & Iversen, 1987) and NMDA, quisqualate, kainate and L-AP4 subclasses have been delineated. Quisqualate and kainate receptors are thought to be associated with rapid signal transduction and thus may be linked closely with Na^+/K^+ channels (class I receptors). NMDA receptors may not always be associated with fast signal transmission, and Ca^{2+} fluxes have also been associated with these receptors. NMDA receptors are sometimes associated with G-proteins (Monaghan & Cotman, 1986) and effects of NMDA and quisqualate receptors on second messenger systems have been described (Sladeczek *et al.*, 1985; Baudry *et al.*, 1986; Nicoletti *et al.*, 1986; Pearce *et al.*, 1986; Sugiyama *et al.*, 1987) so that further subclasses (class II) of these receptors may be eventually described.

GABA

Rapid (30 ms) inhibitory actions of GABA have been described (Barker & McBurney, 1979) and these are consistent with action at $GABA_A$ receptors (blockable by bicuculline) (class I). In rat brain it has been suggested that as many as 30% of the nerve terminals are GABAergic in character (Iversen & Bloom, 1972), so that this would be consistent with GABAergic nerve cells playing a major functional role. Close synaptic interactions have been described (Houser *et al.*, 1985). GABA can also act at $GABA_B$ receptors. These are pharmacologically distinct and appear to be class II receptors linked via G-proteins to second messenger systems (Asano *et al.*, 1985; Hill *et al.*, 1984; Wojcik & Neff, 1984; Watling & Bristow, 1986) and ion channels (Andrade *et al.*, 1986; Scott & Dolphin, 1986). Consistent with this, $GABA_B$ receptors have been reported to be important in the control of transmitter release (Chesselet, 1984).

Glycine

Glycine is an inhibitory transmitter with a rather circumscribed role. Its role as an inhibitory transmitter is established in the spinal cord, and functions in other limited regions have been suggested (Fagg & Foster, 1983). The actions are very rapid (10 ms) (Werman *et al.*, 1967) and this is consistent with a class I receptor based system. Glycine is also reported to perform a modulatory role on the NMDA subclass of glutamate receptors (Cotman & Iversen, 1987).

Acetylcholine

Muscarinic actions of acetylcholine predominate in the central nervous system and are often of a modulatory nature, altering the excitability of other cells consistent with the ideas expressed earlier about the class II nature of muscarinic receptors (Brown, 1986). Muscarinic actions of acetylcholine are generally slow, although the actions do seem to be elicited at synapses (Rotter *et al.*, 1977; Houser *et al.*, 1985), there being little evidence for diffuse actions of acetylcholine. Mechanisms of muscarinic acetylcholine receptors have been outlined above and are entirely consistent with the class II category of receptor.

Actions of acetylcholine at nicotinic receptors have also been described in the brain, and where these have been studied they are rapid (Schmidt, 1979; Schmidt & Freedman, 1980). Nicotinic acetylcholine receptors related to the neuromuscular junction receptors have been isolated from brain tissue (Wang *et al.*, 1978; Oswald & Freeman, 1981; Barnard & Dolly, 1982). One action of nicotinic receptors that has been well validated in the brain is a stimulation of release of dopamine in the striatum (Chesselet, 1984). Given that dopamine release is also stimulated by acetylcholine acting at muscarinic receptors this is somewhat surprising, but perhaps the differential time courses for the two receptors gives flexible control of dopamine release.

Dopamine

The actions of dopamine are typically inhibitory and rather slow (seconds) consistent with a modulatory action via class II receptors (Moore & Bloom, 1978; Reader *et al.*, 1979; Brown & Arbuthnott, 1983). Dopamine is restricted to specific pathways, and at least

in the case of the nigrostriatal dopamine system the pathway branches widely within the striatum making numerous synaptic contacts (Moore & Bloom, 1978; Doucet *et al.*, 1986; Kubota *et al.*, 1987). This would be consistent with the action of dopamine being to modulate function in a broadly based manner within the striatum. Both dopamine receptor subtypes described (D_1 and D_2) fall into the class II category (Strange, 1987) consistent with a slow modulatory action.

Noradrenaline

The actions of noradrenaline are inhibitory and rather slow (50 ms–350 ms) (Moore & Bloom, 1979; Reader *et al.*, 1979), consistent with action via class II receptors. Noradrenergic pathways are characteristically diffuse and widely branching, and although the issue of the frequency of synaptic contacts is controversial (Beaudet & Descarries, 1978; Kosofsky *et al.*, 1984) they seem to act as modulators of function in a wide area, again consistent with a class II receptor based system. In agreement with this idea are the observations of Greengard and colleagues (Mobley & Greengard, 1985) who showed that noradrenaline has a widespread influence on synapsin I phosphorylation in cerebral cortex despite the noradrenergic innervation being sparse. They suggest that this was consistent with noradrenaline acting in a 'paracrine' fashion, released at discrete sites but having effects at receptors some distance away. All the adrenoceptor subclasses described (α_1 α_2, β_1 and β_2) are class II, consistent with the modulatory role described above.

It has been further suggested that catecholamine (dopamine, noradrenaline) circuits do not act as simple inhibitory systems but that rather they act as 'bias' adjusting systems (Bloom, 1979; Moore & Bloom, 1979). This may be again a reflection of the structure–function relationships in class II receptor based systems.

Serotonin

Actions of serotonin have been described that are slow and modulatory and in some studies typical synaptic contacts are not made (Descarries *et al.*, 1975) whereas in others they are (Kosofsky *et al.*, 1984). This would be consistent with a class II receptor based system, and where this information is available the serotonin receptors that have been characterized are of this kind ($5HT_{1A}$, $5HT_2$) (Richardson & Engel, 1986; various authors, 1986).

Histamine

The actions of histamine have been described as modulatory and this transmitter is contained in widely branching neuronal pathways which influence large target fields. Receptors for histamine (H_1,H_2) are of the class II type, consistent with these observations (Pollard & Schwartz, 1987).

Neuropeptides

For the peptide neurotransmitters/neuromodulators there is only partial information available on many of their actions. When their actions are studied electrophysiologically many of these are slow (Hartzell, 1981; Kelly, 1982; North & Egan, 1982), although there are examples of more rapid actions (Kelly, 1982; Duggan, 1983; Iversen, 1983). Receptors for neuropeptides are class II, linked via G-proteins to alterations of adenylate cyclase, phospholipase C or to ion channels (see above).

Some specific examples are as follows. The actions of substance P are slow (Otsuka *et al.*, 1982); some substance P-containing neurones do make synaptic contacts, some do not (Nicoll *et al.*, 1980; Cuello, 1983). Substance P receptors are class II linked to phospholipase C (Mantyh *et al.*, 1984). Opiate peptides also act in a modulatory way with slow actions (Bloom, 1983, although see Duggan, 1983). In some cases synaptic contacts are made by opiate-containing neurones, in other cases they are not (Hamel & Beaudet, 1984). Opiate receptors are class II linked to adenylate cyclase or ion channels via G-proteins (Snyder & Childers, 1979; Hescheler *et al.*, 1987). LHRH has been shown to have very slow electrophysiological actions on frog sympathetic neurones and to act in a diffuse manner (Kuffler *et al.*, 1984). LHRH receptors in the pituitary are class II linked to phospholipase C (Naor *et al.*, 1986).

In the above discussion I have tried to evaluate the evidence for two propositions. Firstly, that fast events in the nervous system are mediated via class I receptors whereas slower events are mediated via class II receptors, and the evidence bears this out well. Secondly, that systems acting via class I receptors function via tight synaptic contacts whereas systems functioning via class II receptors may not have close synaptic contacts and transmitter may be released non-synaptically to act at receptors some distance away. Although there is evidence in support of this proposition, in many cases it seems that synaptic contacts are made for each receptor class.

This latter proposition has been discussed by Vizi (1984) in relation to non-vesicular release of transmitter and is given some support by studies of the relative distributions of transmitter and receptors measured autoradiographically. A 'mismatch' is often seen between the two patterns and it has been suggested that this may be due in part to transmitter being released some distance from its ultimate receptor site (Herkenham & Maclean, 1986). There are in fact many other reasons why a mismatch might occur, and as has been discussed above in many class II receptor-based systems, where the mismatch might be expected, synaptic contacts are made. In addition mismatch has been described for class I receptor systems, so that the existence of a mismatch cannot be taken as evidence of non-synaptic events. Nevertheless it seems that actions of transmitters at non-synaptic sites may be an important phenomenon.

A further point can be made regarding presynaptic receptors i.e. receptors found in the presynaptic terminal whether or not the receptors are for the same transmitter released from the terminal (autoreceptors) or different (Starke, 1981; Chesselet, 1984). Such presynaptic receptors can, when stimulated, alter the ability of the terminal to release transmitter and it might be expected that this would be a slow modulatory action typical of a class II receptor-based system. On the whole, presynaptic receptors are of the class II type as predicted, but there are exceptions. Several reports exist of nicotinic (class I receptor) actions of acetylcholine stimulating transmitter release presynaptically (Chesselet, 1984) and this has been considered above. As a further speculation, it could be that many of the presynaptic (axo-axonic) modulatory actions of transmitters could be via non synaptic interactions and class II receptors.

I have considered neurones as containing a single

transmitter, but this may be an oversimplification given the emerging evidence on coexistence of more than one transmitter in the same neurone (Lundberg & Hokfelt, 1983). This increases the complexity of the interactions both presynaptically and postsynaptically, and some of the ramifications have been discussed elsewhere (Lundberg & Hokfelt, 1983). Mainly the coexisting species are substances that both act via separate class II receptors, e.g. a monoamine and a peptide, but examples of coexistence of GABA (likely to act via class I receptors) and peptides have been described (Kosaka *et al.*, 1987). It is also possible that with coexistence, one substance could act synaptically whereas the other could act more diffusely, depending on the positions of the receptors. This, as well as differences in the mode of termination of action of the released substances, could affect the relative duration of their responses.

In concluding this section it should be becoming apparent that the classification of receptors (class I and class II) may be a reflection of a broader subclassification of the structure and function of the central nervous system into different kinds of circuitry.

DISORDERS OF THE CENTRAL NERVOUS SYSTEM

These considerations have implications for our understanding of diseases of the, nervous system and their treatment. Let us consider first neurological diseases where clear losses of nerve cells have been described.

Parkinson's disease

In this disorder there is clear evidence for a major loss of dopamine neurones in the nigrostriatal dopamine pathway and this loss seems to be associated with at least some of the clinical manifestations (Green & Costain, 1981). The motor dysfunctions of Parkinson's disease may be alleviated by therapy with L-dihydroxyphenylalanine ('L-DOPA') (converted to dopamine in the brain) or a dopamine agonist such as bromocryptine. Success with the latter approach implies that normal function may be restored simply by occupancy of the postsynaptic receptors by an agonist. As the agonist must be available to the receptors at a steady concentration dependent on the dose used, this implies that the normal function of the system may be similar: dopamine is normally released to provide a certain concentration sufficient to occupy an appropriate fraction of the postsynaptic receptors. Release is not in specific bursts or coded temporally and this is consistent with earlier discussions regarding the nigrostriatal pathway and the function of the postsynaptic receptors (D_1 and D_2 dopamine) which are of the class II type.

Recent observations on Parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine ('MPTP') are consistent with this idea (Calne *et al.*, 1985; Snyder, 1985). Considerable damage can occur to the nigrostriatal pathway before symptoms of Parkinsonism are apparent, and it has been estimated that up to 70% of the pathway may be destroyed before symptoms are manifest (Snyder, 1985). This is again consistent with the idea that the pathway functions to release a tonic level of dopamine and that there is considerable redundancy.

It seems reasonable to suppose based on the above arguments that some of the released dopamine diffuses to sites distant from the release site and the functions of the postsynaptic receptor are to provide highly specific recognition of dopamine and the appropriate intracellular response. These ideas are further supported by animal experiments where alterations of striatal neuronal activity are only seen after destruction of greater than 90% of the nigrostriatal dopamine neurones (Orr *et al.*, 1986). This is partly due to compensating proliferation of postsynaptic receptors and increased dopamine release (which probably also occur in Parkinson's disease), but again suggests that the effects of dopamine on striatal activity may be widespread and may not be confined to specific synaptic contacts.

It should be apparent, therefore, that one reason it is possible to treat Parkinson's disease with L-DOPA is because of the relative simplicity of the actions of dopamine normally. Thus decarboxylation of L-DOPA within the brain provides a concentration of dopamine sufficient to make up for that lost via neuronal degeneration. Similarly these ideas offer optimism for the use of neuronal transplants in Parkinson's disease (for a review see Snyder, 1987) where it should be sufficient to provide a tonic rather than a phasic or coded release of transmitter.

Alzheimer's disease

Intensive neurochemical and neuropathological investigations of Alzheimer's disease have identified ascending cholinergic pathways from the nucleus basalis of Meynert to the cerebral cortex as being defective (Bowen & Davidson, 1986). The association of cholinergic pathways with memory and cognition suggested that the cholinergic deficit might be critical for the cognitive changes seen in Alzheimer's disease (Coyle *et al.*, 1983).

Extensive attempts to increase cholinergic function by treating patients with precursors of acetylcholine, inhibitors of acetylcholine breakdown or direct-acting cholinergic agonists have been largely unsuccessful. This contrasts strongly with the success of dopamine replacement therapy in Parkinson's disease. The lack of success is likely to be due to the occurrence of other pathway losses in Alzheimer's disease but may also be related to the normal function of the cholinergic pathways from the nucleus basalis to the cerebral cortex. These seem to be arranged in a topographically discrete manner (Price & Stern, 1983) and function in bursts in response to particular behaviour (Richardson & Delong, 1986). The physiology of the pathway is not well understood but it may perform an enabling function during certain discrete behaviours. The topographically and temporally discrete nature of the pathway means that despite the fact that it is assumed to function via muscarinic acetylcholine (class II) receptors (Coyle *et al.*, 1983) it will be very difficult to replace function once neurones are lost.

Very recently it has been suggested that the primary defect in Alzheimer's disease, preceding the cholinergic changes, may be in cortical glutamatergic pathways and that these changes may be relevant to cognition (Mann *et al.*, 1985; Bowen & Davidson, 1986; Hardy *et al.*, 1987). If this proves to be the case then the critical alterations of neuronal function may be occurring in a glutamatergic, class I receptor-based system. Owing to the normal rapid phasic action of this pathway little scope can be envisaged for replacement therapy unless

this can be done in such a way as to mimic normal function.

In summary, for neurological diseases where the degeneration is occurring in a pathway dependent on class II receptors, therapy based on replacement of the deficient transmitter exogenously may be effective, as in Parkinson's disease, whereas if a pathway dependent on class I receptors is affected replacement is likely to be less effective unless this can be done in such a way that the normal pattern of information is restored. This is unlikely to be achieved by exogenous addition of the deficient transmitter.

Psychiatric disorders

For the psychiatric disorders (see Green & Costain, 1981), where no evident losses of nerve cells occur, there must be some alterations of normal function and therapy should be possible based on altering the functional activity of the system. For schizophrenia some of the symptoms may be alleviated by the antipsychotic drugs whose primary site of action seems to be the D_2 dopamine receptor, a typical class II receptor. In depression, drugs that alter functional activities of noradrenaline or serotonin seem effective and these are class II receptor-based systems. In addition lithium carbonate used for treating manic depressive illness interferes with the inositol phospholipid signalling system (linked to class II receptors). Alterations in the activity of these class II receptor-based pathways in turn affect class I receptor-based pathways. In treatments for anxiety a class I receptor is modulated directly. Benzodiazepines and barbiturates modulate allosterically the activity of the $GABA_A$ receptor/chloride ion channel complex (Olsen, 1981; Stephenson, 1985) a key component of a class I receptor based system. It may be predicted that similar modulation of glutamate receptors (class I) will be possible offering scope for the design of new drugs (see for example, Cotman & Iversen, 1987).

CONCLUSION

In summary, therefore, receptors in the central nervous system may be divided into class I (fast) and class II (slow) and these classes are structurally and functionally distinct. Circuitry in the central nervous system can also be divided structurally and functionally into fast and slow groups. The two subclassifications are interdependent and have implications for the understanding and treatment of brain disease.

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