may be. This assortment of ingredients is combined in the mathematical equivalent of a witches' cauldron to produce a powerful potion, an algebra of 196,884 dimensions which is '99 per cent associative' (see below). Three groups of symmetries of this algebra are defined, related by a remarkable 'triality' property of Parker's loop. The monster, like Gaul, is made up from these three parts. Its finiteness is almost a triviality. The proof is an intricate virtuoso performance, typical of its inventor, and it represents a major demystification of both the monster and the sporadics.

It also casts an interesting light on the traditional way to find 'interesting' algebras, which is basically to state new systems of laws and to look for algebras that obey them. The algebra for the monster is not defined in this way — it is like a fine upstanding citizen given to minor criminal tendencies. A random triple (x,y,z) chosen from this algebra has about a 99 per cent chance of obeying the associative law, but the other 1 per cent flout it, apparently with a clear conscience. This curious and tantalizing fact suggests a re-examination of the principles by which interesting algebras are identified. Is the time ripe for a theory of 'almost laws' of algebra? □

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Neurotransmitters

Modifying channel function

from Charles F. Stevens

THREE recent articles — one on page 670 of this issue[1] and two[2,3] in an earlier issue — shed light on one of the brain's most remarkable features: its ability to modify itself. Neurotransmitters bound to the surface receptors on neurones can cause the electrical excitability of the cell to change. All three reports present evidence that a coupling protein, G protein, forms the link between surface receptors and the alteration of properties of ionic channels that produce a change in the excitability of the cell. Unlike the best studied neuromodulatory systems, the mechanism does not involve changes in the concentration of cyclic (c) AMP or other second messengers in the cytoplasm; this chemical signalling system is limited to messenger molecules diffusing within the surface membrane of the cell.

Computers are self-modifying in that they sometimes alter their own programs, but the self-modifiability of the brain goes much further: the hardware itself is modified. One neurone applies a neurotransmitter to the surface of another; this transmitter can cause some of the ion channels on the second neurone to be covalently modified. Because the computing properties of a neurone are determined by the characteristics of its various ion channels, one neurone can change the way a second processes information.

The 'usual' way to modify channels — that is, the one we know most about — is to phosphorylate them with cAMP-dependent protein kinase[4]. The cAMP cascade has five main steps: (1) neurotransmitter binds to the cell surface; (2) bound receptor activates the enzyme adenylate cyclase that in turn (3) makes cAMP from ATP; (4) this cAMP activates the kinase that (5) adds a phosphate group to specific sites on the channel. Once it is phosphorylated the channel behaves differently; it may open less often or may stay open longer each time it is activated depending on what sort of channel it is.

G proteins form a family with at least four members: two of these, G_s and G_i (sometimes called N_s and N_i), either stimulate (G_s) or inhibit (G_i) the adenylate cyclase. They in turn are activated by neurotransmitters binding to other receptors. The G proteins, then, are the messengers that tell the cyclase how active it should be according to which neurotransmitter receptors are occupied.

Why are the neuromodulatory cascades so complicated? Three reasons, at least. First, the same basic cascade can be used in different cells with only small changes — for example, the specificity of the receptor can be changed while the remainder of the system is kept the same. Second, each step can amplify the signal: one receptor can activate many enzymes by using the G-protein intermediate. Finally, the multiple steps provide many places where regulatory systems can interact. For example, stimulation of an enzyme by one neurotransmitter through G_s can be antagonized by the action of a second neurotransmitter through G_i.

The three recent papers all show that neurotransmitters act through a G protein, but that the traditional cAMP system is not involved. The two earlier studies[2,3] demonstrated that acetylcholine, which causes inhibition of the heart, works through a G protein that turns on a special set of potassium channels. The article in this issue[1] shows that calcium channels in dorsal root ganglion neurones are turned off by noradrenaline and by γ-aminobutyric acid (usually an inhibitory neurotransmitter) acting through a G protein.

How are the channels turned on or off by G proteins? One speculative possibility is that the G protein works directly on the channel just as, in other instances, it works on enzymes such as adenylate cyclase. If a G protein can modify enzyme function, why not channel function? A second possibility, for which there is some preliminary evidence[5], is that another regulatory cascade is operating, one that involves the protein C kinase, to phosphorylate channels. The protein C kinase cascade also uses one or more members of the G-protein family, but its signalling molecule would be, in this context, diacylglycerol produced by a phospholipase, rather than cAMP made by adenylate cyclase as in the cAMP cascade. Whether the mechanism involves the direct action of G proteins on the channels or phosphorylation of channels by the protein C kinase (or some yet more mysterious alternative) must be decided by additional experiments.

When it was believed that neuromodulation generally worked by phosphorylation through the cAMP cascade everything seemed relatively simple, but now the story is getting more complex. Probably this is just the start: phosphorylation by many different kinases, direct regulation by G proteins, different second-messenger systems and regulation through GTP levels as well as through phosphatases are all likely to be involved in the brain's intricate regulation of its own properties. □

1. Holz, G.G., Rane, S.G. & Dunlap, K. *Nature* **319**, 670 (1986).
2. Pfaffinger, P.J., Martin, J.M. Hunter, D.D., Nathenson, N.M. & Hille, E. *Nature* **317**, 536 (1985).
3. Breitwieser, G.E. & Szabo, G. *Nature* **317**, 538 (1985).
4. Levitan, I.B. *J. memb. Biol.* **87**, 177 (1985).
5. Rane, S.G. & Dunlap, K. *Proc. natn. Acad. Sci. U.S.A.* **83**, 184, (1986).

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More stamps for Halley's comet

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