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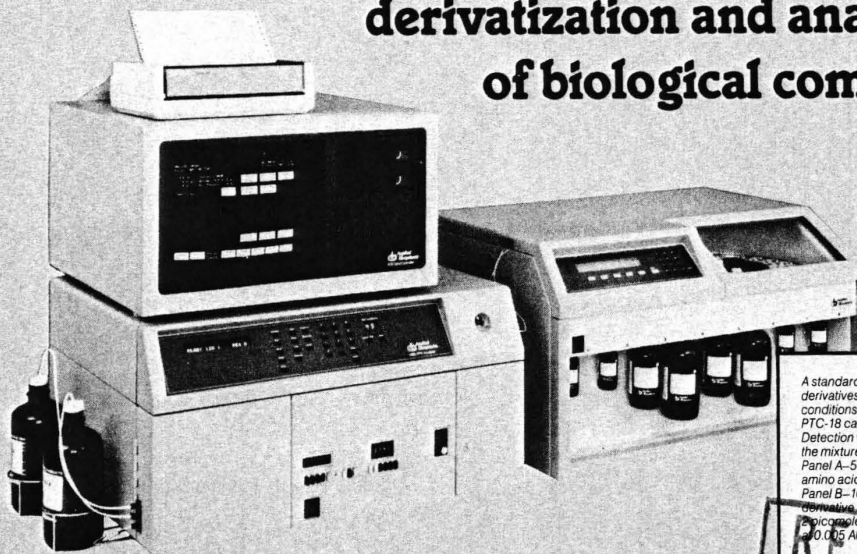
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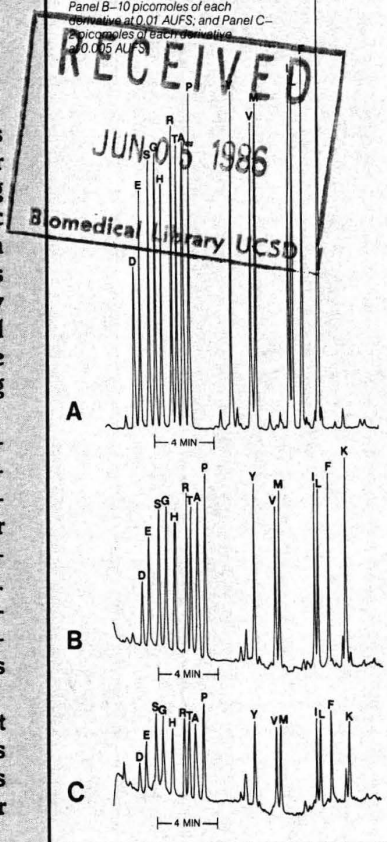
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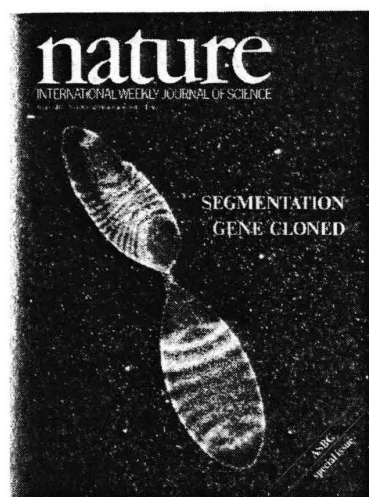
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# nature

NATURE VOL. 321 29 MAY 1986



Expression of the *Drosophila* pair-rule gene *paired* in blastoderm (lower) and gastrulation (upper) stage embryos. As explained on page 493 of this issue, although *paired* has been classed as a pair-rule gene on the basis of the two-segment periodicity in the pattern elements deleted in *paired* mutants, in its final form the striped pattern of *paired* gene expression has twice this periodicity. This and related work is reviewed in News and Views on page 472.

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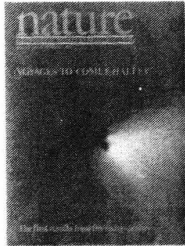
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differed between NMDA and KA (Fig. 3c, d), and in individual spinal cord neurones KA-evoked increases in  $[Ca^{2+}]_i$  were always much smaller than those evoked by NMDA. These experiments suggest that  $Na^+$  is a poor trigger for inducing an increase in  $[Ca^{2+}]_i$ , since in several neurones the inward ( $Na^+$ ) current activated by KA produced no detectable arsenazo III signal. However, our results do not exclude the possibility that  $Ca^{2+}$  influx through ion channels activated by NMDA triggers release of  $Ca^{2+}$  from intracellular stores<sup>27</sup>, contributing further to the NMDA-evoked arsenazo III signals reported here. Although the present results suggest a high  $Ca^{2+}$  permeability of NMDA-receptor-activated channels (Fig. 3), the net flux of monovalent cations (that is, conductance) decreases in the presence of  $Ca^{2+}$ . This reflects interactions between permeant ions within the channel with  $Ca^{2+}$  acting as both a permeant ion and as a blocker of monovalent cation flux<sup>25,26,28</sup>.

The experiments reported here provide evidence for an agonist-triggered increase in  $[Ca^{2+}]_i$  in mammalian spinal cord neurones. Previously, ion-sensitive microelectrodes were used to measure changes in intracellular ionic activity triggered by excitatory amino acids in frog motoneurons<sup>9</sup>. The latter experiments suggested an increase in both  $[Na^+]_i$  and  $[Ca^{2+}]_i$  during perfusion with L-glutamate but the results were difficult to interpret clearly as (1) neurones were not voltage-clamped and thus it is difficult to separate the relative contributions of  $Ca^{2+}$  influx via voltage-dependent calcium channels and agonist-activated channels, and (2) L-glutamate is a mixed agonist that acts at multiple subtypes of excitatory amino-acid receptor<sup>2,6,7</sup>.

The response to NMDA-receptor activation thus provides a second source of calcium flux, distinct from that resulting from conventional voltage-dependent calcium channels, which may have important long-term effects on excitability. Our finding that the ion channels linked to the NMDA receptor subtype are more permeable to  $Ca^{2+}$  than those linked to KA receptors, has implications for the role of excitatory amino-acid receptors in CNS function. It is possible that  $Ca^{2+}$  influx activated by NMDA receptors underlies the synaptic plasticity generating long-term potentiation, as the latter is prevented by intracellular injection of EGTA to chelate  $Ca^{2+}$  (ref. 29), or by blocking NMDA receptors with selective antagonists<sup>30</sup>. For example,  $Ca^{2+}$  influx localized at transmitter-operated ion channels could have a role in organizing and regulating postsynaptic structures in an appropriate spatial relation to transmitter-releasing presynaptic terminal boutons, and it is important to consider that  $Ca^{2+}$  influx occurring at NMDA receptors located on dendritic spines might produce an especially large but localized elevation in intracellular  $Ca^{2+}$  concentration, due to restriction of  $Ca^{2+}$  diffusion along the narrow shaft of the spine. In addition, our results have some bearing on the mechanisms of desensitization of NMDA receptors, as the link that has been demonstrated between  $[Ca^{2+}]_i$  and desensitization of nicotinic receptors at the neuromuscular junction<sup>31,32</sup> may occur also for other receptor-ionophore complexes. Thus our results may help to explain the similar desensitization evoked by either large doses of NMDA or depolarizing voltage jumps<sup>7</sup>, which trigger  $Ca^{2+}$  entry through NMDA channels and voltage-dependent calcium channels, respectively.

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## Replacing the complementarity-determining regions in a human antibody with those from a mouse

Peter T. Jones, Paul H. Dear, Jefferson Foote, Michael S. Neuberger & Greg Winter

Laboratory of Molecular Biology, Medical Research Council, Hills Road, Cambridge CB2 2QH, UK

The variable domains of an antibody consist of a  $\beta$ -sheet framework with hypervariable regions (or complementarity-determining regions—CDRs) which fashion the antigen-binding site. Here we attempted to determine whether the antigen-binding site could be transplanted from one framework to another by grafting the CDRs. We substituted the CDRs from the heavy-chain variable region of mouse antibody B1-8, which binds the hapten NP-cap (4-hydroxy-3-nitrophenacetyl caproic acid;  $K_{NP-cap} = 1.2 \mu M$ ), for the corresponding CDRs of a human myeloma protein. We report that in combination with the B1-8 mouse light chain, the new antibody has acquired the hapten affinity of the B1-8 antibody ( $K_{NP-cap} = 1.9 \mu M$ ). Such 'CDR replacement' may offer a means of constructing human monoclonal antibodies from the corresponding mouse monoclonal antibodies.

The three-dimensional structures of several immunoglobulins show that the variable domains consist of two  $\beta$ -sheets pinned together by a disulphide bridge, with their hydrophobic faces packed together<sup>1-3</sup>. The individual  $\beta$ -strands are linked by loops which at one tip of the  $\beta$ -sheet may fashion a binding pocket for small haptens<sup>1,2</sup>. Sequence comparisons among heavy- and light-chain variable domains ( $V_H$  and  $V_L$  respectively) reveal that each domain has three CDRs flanked by four relatively conserved regions (framework regions—FRs)<sup>4</sup>. As seen in the structure of the human myeloma protein NEWM (Fig. 1), the CDRs include each of the three main loops. Often the CDRs also include the ends of the  $\beta$ -strands, suggesting that side chains at the ends of the  $\beta$ -strands may help to fix the conformation or orientation of the loops. The framework regions form the bulk of the  $\beta$ -sheet, although for example in the  $V_H$  domain of NEWM, FR1 includes part of the loop between the two  $\beta$ -sheets and CDR2 not only forms a loop but a complete  $\beta$ -strand (Fig. 1). The structure of the  $\beta$ -sheet framework is similar in different antibodies, as the packing of different side chains is accommodated by slight shifts between the two  $\beta$ -strands<sup>5</sup>. Furthermore, the packing together of  $V_L$  and  $V_H$  FRs is conserved<sup>6</sup>, therefore the orientation of  $V_L$  with respect to  $V_H$  is fixed. We wondered whether the FRs represent a simple  $\beta$ -sheet scaffold on which new binding sites may be built, and

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