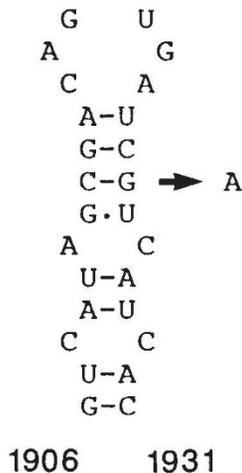


Alzheimer's mutation

SIR — It has recently been shown¹ that affected individuals in two familial Alzheimer's disease pedigrees contain a base substitution in the gene encoding the amyloid beta protein precursor (APP) located on chromosome 21. This substitution replaces a G with an A at position 1924 of APP (according to APP695 sequence)², resulting in the production of an isoleucine in place of a valine at residue 642 in the transmembrane domain. The authors speculate that the slightly more hydrophobic isoleucine residue may alter the anchoring of APP in the membrane¹.

We offer an alternative hypothesis, and suggest that this mutation disrupts a regulatory stem loop structure in APP messenger RNA. Flanking the mutation site are 26 nucleotides capable of forming a stem loop structure (base pairs 1906–1931, see figure).



The stem loop formed by nucleotides 1906–1931 of APP (APP 695 nomenclature). The CAGUGA loop matches a consensus sequence of iron-responsive elements, and so may be a site of translational regulation of APP. The substitution of G to A at position 1924 destabilizes the stem, disrupting this structure⁵.

This loop contains the consensus sequence CAGUGA characteristic of the iron-responsive elements (IRE) present in the genes encoding ferritin and the transferrin receptor³. These elements interact with a common binding protein which regulates protein production at the translational level in response to iron concentration. In both the ferritin and transferrin receptor genes, the IREs are contained in noncoding regions. In APP an IRE-like stem loop appears precisely at residue 40 of the beta/A4 peptide. By analogy, the putative IRE stem loop in APP may be a translational regulatory element which governs APP production.

The stem consists of ten bases on either side. Eight nucleotides on each arm form base pairs with the complementary side (including one G·U pair). The base substitu-

tion at position 1924 destroys the third of three consecutive base pairs directly under the loop, thereby destabilizing the stem (see figure).

Patients heterozygous for this mutation may lose the ability to regulate normally translation of APP and so produce abnormally high amounts of protein product. This would lead to elevated levels of APP in these patients similar to those observed in patients with Down syndrome who, presumably owing to the presence of a third copy of the gene, form substantial amounts of amyloid by middle age⁴.

Translational regulation of APP message by a protein similar to the IRE-binding protein would allow both environmental and genetic factors to influence APP production. Modulation of a translational regulatory

Homeostatic muffling

SIR — In the brain many mechanisms help to minimize local ionic changes in response to a sudden change in neuronal activity. We suspect that our understanding of these mechanisms has been hindered by the inappropriate use of the term 'buffer' to describe them. We propose an alternative to clarify future discussion.

The term buffer was originally introduced to describe the reversible reaction between H⁺ ions and weak acids or bases. Its meaning was later extended to cover the chemical buffering of Ca²⁺, and then, more boldly, to describe the carriage of K⁺ by glial cells away from a site of excess production as "spatial buffering"¹. Although this later extension may have been paradoxically justifiable, as K⁺ is not chemically buffered², it has led to more extensive use of the term buffer to describe processes other than chemical buffering.

In order to reduce confusion, we propose that all processes minimizing ionic activity changes (and for H⁺ and Ca²⁺ these include buffering) be included in the term, 'muffling', and that 'buffering' be confined to chemical buffering.

To exemplify this we describe an experiment in which we used a double-barrelled pH microelectrode to follow extracellular potential and pH in an isolated leech ganglion, as described elsewhere³, and tested H⁺ muffling by brief applications of ammonium ions. The addition and removal of NH₄⁺ caused biphasic changes of extracellular pH (pH_e) as NH₃ is much more permeant through cell membranes than NH₄⁺. In HEPES-buffered solution the test caused a pH_e swing of 0.34.

When a CO₂/bicarbonate solution was applied, pH_e increased to over 7.4, and two tests of muffling caused pH_e swings of only about 0.1. Thus muffling power had more than trebled. After acetazolamide application, however, the pH_e swing increased to 0.26, indicating that muffling power is

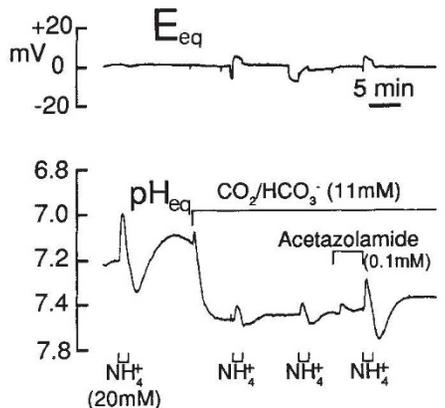
reduced by inhibiting carbonic anhydrase. This confirms earlier reports^{4,5} of a role for carbonic anhydrase in extracellular H⁺ homeostasis. So bicarbonate and its rapid

RUDOLPH E. TANZI
BRADLEY T. HYMAN

The Molecular Neurogenetics Laboratory and The Laboratory of Experimental Neuropathology, Department of Neurology, Massachusetts General Hospital, Fruit Street, Boston, Massachusetts 02114, USA

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Potential and pH of extracellular space in an isolated leech ganglion showing responses to ammonium applications.

conversion to CO₂ is important in extracellular H⁺ muffling, which will include local buffering, diffusion of H⁺ and buffer ions, membrane transport and intracellular muffling, including intracellular buffering.

ROGER C. THOMAS
Department of Physiology, University of Bristol, School of Medicine, University Walk, Bristol, BS8 1TD, UK

JONATHAN A. COLES
INSERM U176, F-33077, Bordeaux, France

JOCHEN W. DEITMER
FB Biologie der Universität, D-6750, Kaiserslautern, Germany

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