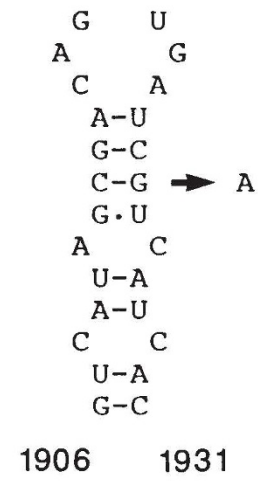
# Alzheimer's mutation

SIR — It has recently been shown[1] 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 membrane[1].

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 destablizes the stem, disrupting this structure[5].

This loop contains the consensus sequence CAGUGA characteristic of the iron-responsive elements (IRE) present in the genes encoding ferritin and the transferrin receptor[3]. 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 substitution at position 1924 destroys the third of three consecutive base pairs directly under the loop, thereby destablizing 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 age[4].

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 element would be an attractive target for therapeutic intervention.

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# Homeostatic muffling

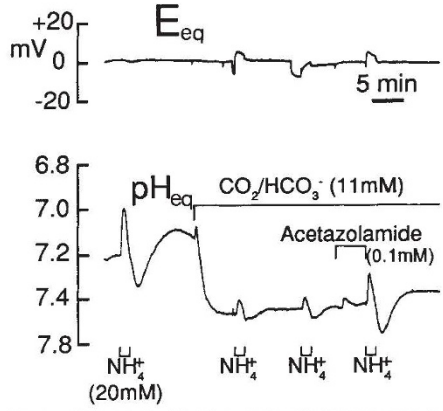
SIR — In the brain many mechanisms help to minimize local ionic changes in response to a sudden change in neuronal activity. We suspect that our understanding of these mechanisms has been hindered by the inappropriate use of the term 'buffer' to describe them. We propose an alternative to clarify future 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 $Ca^{2+}$, 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 buffered[2], 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 $Ca^{2+}$ 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 elsewhere[3], and tested $H^+$ muffling by brief applications of ammonium ions. The addition and removal of $NH_4^+$ caused biphasic changes of extracellular pH ($pH_e$) as $NH_3$ is much more permeant through cell membranes than $NH_4^+$. In HEPES-buffered solution the test caused a $pH_e$ swing of 0.34.

When a $CO_2$/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 conversion to $CO_2$ 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.




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

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