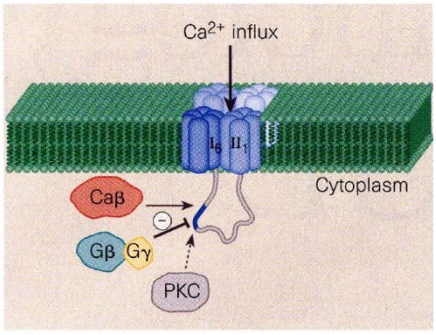

Figure 1 **Several classes of Ca^{2+} channel exist (A, B, C, D, E and S). They all contain a transmembrane α_1 subunit that is made up of four homologous repeats (I–IV), each of which comprises six putative membrane-spanning helices. The intracellular cytoplasmic 'linker' domain is a stretch of >100 amino acids that links helix 6 of repeat I (I_6) to helix 1 of repeat II (II_1). The highlighted region of this I–II linker is a hot-spot for molecular integration — it binds Ca^{2+}-channel β subunits (Caβ) which enhance channel function. Both Zamponi *et al.*[2] and De Waard *et al.*[3] have shown that in class A, B and E channels it also binds G-protein βγ-subunit complexes (Gβγ), which inhibit channel function. Additionally, phosphorylation of this domain by protein kinase C (PKC) eliminates Gβγ-mediated inhibition of the Ca^{2+} current.**

Gα or Gγ alone) bind to the cytoplasmic linker region that is found between transmembrane repeats I and II (Fig. 1) of some Ca^{2+}-channel classes (α_{1A}, α_{1B} and α_{1E}) but not of others (α_{1C}, α_{1D} and α_{1S}).

De Waard *et al.*[3] noted that the amino-terminal region of the I–II linker contains a sequence that includes the QXXER sequence, which is essential for Gβγ to bind to adenylyl cyclase[8]. By mutating Q and R in this domain, along with several flanking amino acids, they were able to prevent the binding of Gβγ to this region of the I–II linker protein derived from the α_{1A} Ca^{2+} channel. Interestingly, a second (carboxy-terminal) region of the α_{1A} I–II linker also binds Gβγ, even when the amino terminus is mutated.

Electrophysiological recordings allowed the two groups to move from the realm of protein-binding assays to that of physiological function. Zamponi *et al.*[2] showed that when peptides containing the QXXER sequence are injected into cells, they interfere with Gβγ-mediated inhibition of α_{1A} and α_{1B} Ca^{2+} currents. Taking this a step further, De Waard *et al.*[3] found that the point mutation in α_{1A} that eliminates Gβγ binding to the amino terminus of the I–II linker also prevents the G-protein-dependent inhibition of α_{1A} currents that occurs when G proteins are directly activated by GTPγS. So the direct binding of Gβγ to the Ca^{2+}-channel α_1 subunit seems to promote a voltage-dependent inhibition of current that is conserved among class A, B and E channels, but not among class C, D or S channels.

The I–II linker domain has other functions within Ca^{2+} channels. The Ca^{2+}-channel β subunit interacts with the α_1 subunit I–II linker and enhances the Ca^{2+} current[9] (Fig. 1). Together with these data, the new findings[2,3] provide a structural explanation for the observation that the β subunit interferes with G-protein-mediated inhibition of Ca^{2+}-channel function[10]. Zamponi *et al.* show that some of the I–II linker peptides that interrupt channel modulation by G proteins are also substrates for protein kinase C. Phosphorylation of these peptides *in vitro* reduces their ability to inhibit G-protein-dependent modulation. This explains why, in some cells, activation of protein kinase C can prevent the voltage-dependent inhibition of Ca^{2+} currents that is produced by transmitters[11].

Some of the new results provide additional food for thought. First, the function of the carboxy-terminal binding site in the I–II linker is not known. De Waard *et al.*[3] report that the binding of Gβγ to this site is unaffected by a mutation elsewhere which eliminates G-protein-dependent inhibition. Paradoxically, Zamponi *et al.*[2] find that G-protein-mediated inhibition is blocked by a peptide from this carboxy-terminal I–II linker. Moreover, a second peptide that is derived from an amino-terminal domain which — according to De Waard *et al.* — does not bind Gβγ, also interrupts G-protein-mediated inhibition. The mechanisms of peptide action, and whether these sequences in the intact channel protein bind Gβγ and/or regulate function, are unknown.

Second, transmitter-mediated inhibition seems to be more effective than that produced by the direct application of purified Gβγ to Ca^{2+} channels. Furthermore, even at very high concentrations of Gβγ[6,7,12], α_{1B} currents are modulated more effectively than are α_{1A} or α_{1E} currents[2,3]. Finally, the function of the Ca^{2+}-channel β subunit and its potential role in influencing the relative sensitivity of α_1 subunits to modulation by Gβγ are unknown.

We have much to learn, as evidenced by a recent paper from Tsien and co-workers[12] whose results seem to contradict those reported here. Tsien's group expressed Ca^{2+}-channel-protein chimaeras in *Xenopus* oocytes to investigate the domains necessary for G-protein-mediated inhibition. They found that replacing the I–II linker from α_{1B} with that from α_{1C} — a channel not inhibited by G proteins — had no effect on G-protein-mediated inhibition of α_{1B} currents. To eliminate G-protein-mediated inhibition, they had to replace both the I–II linker and a second domain in the α_{1B} carboxy terminus with the equivalent domains from α_{1C}. So, in their studies, many sites were essential for G-protein-dependent inhibition.

It seems unlikely that this discrepancy

100 YEARS AGO

Mr. J. Ll. Williams has a very curious note in the number of the *Journal of Botany* for January, on the drunken habits of certain humble-bees. The intoxicant is the honey produced by the crowded flowers of the capitulate heads of certain Compositæ (*Carduus nutans* and *lanceolatus*, and *Centaurea scabiosa*), and Dipsacaceæ (*Scabiosa succisa*). The intoxication is indicated by rolling on the back, striking the legs wildly in the air, and general helplessness. The bees rapidly recovered from the effects, and, in most cases, were eager to repeat the debauch; but one individual, which had been shut up in a vasculum with copious supplies of *Centaurea scabiosa*, manifested, the next morning, a praiseworthy remorse and disgust, "raising its head and fore-legs as high as it could above the plants, then precipitately hurrying away as soon as released." The most dissolute species appears to be the neuter of *Bombus lapidarius*. The author suggests that this may in time become a normal mode of cross-pollinating the flowers in question.
From *Nature* 28 January 1897.

50 YEARS AGO

Dr. A. Parker, director of fuel research, Department of Scientific and Industrial Research, speaking on "Oil from Coal in Germany" at the Fuel Luncheon Club on January 23, stated that Germany developed before the War two synthetic processes, hydrogenation and the Fischer–Tropsch process for the production of petroleum from coal, and many large plants were constructed. At the time of maximum production during the early months of 1944, these two processes together provided oil at a rate of nearly four million tons a year.... Dr. Parker stated that bombing attacks between May and September 1944 caused a reduction in German production of synthetic oil from a rate of nearly four million tons a year to only about 300,000 tons. During the following months, with a reduction in bombing and determined efforts in Germany to repair damage, production again rose to a rate of one million tons a year in November 1944, after which it again fell to 150,000 tons a year at the end of February 1945. It is certain that this systematic destruction of German oil plants was one of the main factors in hastening the defeat of Germany.
From *Nature* 1 February 1947.