Ca^{2+} signals by VDCCs may not be universal, as it appears that VDCCs are not involved in Ca^{2+} influx in response to BDNF in mammalian neurons[2].

So how do chemotropic gradients of netrin or BDNF thereby orient axon growth? As has been shown previously, Wang and Poo[1] and Li *et al.*[2] find that local application of these guidance cues results in a localized increase in intracellular Ca^{2+} on one side of growth cones, because of local Ca^{2+} release from stores and influx through TRP channels. Blocking either release or influx prevents turning, suggesting that both are necessary. This was elegantly demonstrated using a technique known as RNA interference to eliminate a specific subset of TRP channels.

However, this conclusion is slightly ambiguous, because it is often difficult to alter Ca^{2+} release from stores without affecting Ca^{2+} influx, and vice versa. This is certainly true when blocking Ca^{2+} release, which is required to stimulate influx through TRP channels. And it might also be true of blocking TRP-channel activity, which may be required to fill intracellular Ca^{2+} stores. The distinction between Ca^{2+} release and influx is important, as it is uncertain whether both pathways activate similar downstream targets that affect growth-cone motility, leading to turning. Future studies should investigate the specific effects of Ca^{2+} release versus influx on Ca^{2+}-activated molecular targets and the behaviour of growth cones.

With the findings of Wang and Poo[1] and Li *et al.*[2], the signalling cascade responsible for chemotropic axon guidance has gained an important new player: the TRP channel. Many questions remain unanswered, however. For example, it is not known how the receptors for netrin and BDNF stimulate phospholipase C to produce IP_3. Further downstream, the targets of the Ca^{2+} signals that are generated by initial Ca^{2+} influx and release are also uncertain, although protein kinase C, CaMKII and calpain[6–8] are candidates. Processes that are directly responsible for turning growth cones probably ultimately involve local regulation of the cellular skeleton, and perhaps endocytotosis or exocytosis (mechanisms that ingest or extrude membrane) as well. These processes all involve proteins of the Rho family. So it is likely that Ca^{2+} signals ultimately modulate the activity of Rho proteins locally to stimulate axon outgrowth up gradients of netrin and BDNF[6].

Interestingly, under some conditions, netrin and BDNF can also act as chemorepellants, directing growth cones down a concentration gradient. Under these conditions, it has been suggested that a shallower intracellular Ca^{2+} gradient will activate different downstream targets that promote repulsive turning[7,9]. One possible mechanism that could produce a smaller local Ca^{2+} increase is the modulation of Ca^{2+} currents through VDCCs by cyclic nucleotides (via PKA)[10]. However, because VDCCs do not appear to be involved in the chemotropism of mammalian axons, other channels may be modulated instead of these. One possibility that arises from the new findings[1,2] is that TRP channels might be modulated by cyclic nucleotides to control the amplitude of Ca^{2+} gradients within growth cones. And no doubt other channels and molecular targets await

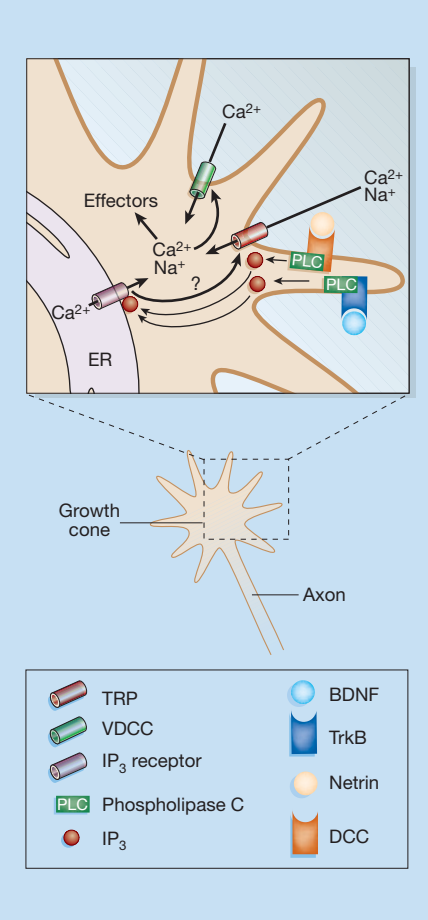

Figure 1 **Calcium signals and axon guidance. TrkB and DCC — receptors for two axon-guidance cues, brain-derived neurotrophic factor (BDNF) and netrin, respectively — are believed to activate phospholipase C, which generates inositol-1,4,5-trisphosphate (IP_3) through lipid hydrolysis. IP_3 stimulates Ca^{2+} release from intracellular stores (such as the endoplasmic reticulum, ER) through IP_3 receptors. Wang and Poo[1] and Li *et al.*[2] show that Ca^{2+} release activates TRP channels, which allow influx of both Ca^{2+} and Na^+. Influx of Na^+ depolarizes the neuron sufficiently to activate voltage-dependent Ca^{2+} channels (VDCCs), further enhancing Ca^{2+} influx. If these Ca^{2+} signalling pathways are activated disproportionately on one side of a growth cone, as occurs when there is a concentration gradient of guidance cues, local activation of Ca^{2+}-dependent effector molecules will occur, turning the axon in the appropriate direction.**

100 YEARS AGO

"The Dynamical Theory of Gases." In Mr. Jean's valuable work on this subject he attacks the celebrated difficulty of reconciling the "law of equipartition of energy" with what is known respecting the specific heats of gases. Considering a gas the molecules of which radiate into empty space, he shows that in an approximately steady state the energy of vibrational modes may bear a negligible ratio to that of translational and rotational modes. I have myself speculated in this direction; but it seems that the difficulty revives when we consider a gas, not radiating into empty space, but bounded by a perfectly reflecting enclosure. There is then nothing of the nature of dissipation; and, indeed, the only effect of the appeal to the aether is to bring in an infinitude of new modes of vibration, each of which, according to the law, should have its full share of the total energy. I cannot give the reference, but I believe that this view of the matter was somewhere expressed, or hinted, by Maxwell. We know that the energy of aetherial vibrations, corresponding to a given volume and temperature, is not infinite or even proportional to the temperature. For some reason the higher modes fail to assert themselves. RAYLEIGH

From *Nature* 13 April 1905.

50 YEARS AGO

Sir Alexander Fleming, the discoverer of penicillin, died suddenly on March 11 at his home in London… The First World War directed his attention to wound infection and its control; he was one of the first to show that most wounds become infected *after* admission to hospital… In 1922 came the discovery of lysozyme. Following an observation that his own nasal secretion after a common cold had an inhibitory action on some of the bacteria present in the nose, he showed that this lytic substance was present in many tissues and secretions of the body… His work with lysozyme prepared the way for the epoch-making discovery of penicillin. Fleming had been studying variation in the staphylococcus, which meant that he was frequently examining colonies of that organism as they appeared on ordinary nutrient agar. As a result of this exposure, a mould appeared on the culture medium some days later and Fleming noticed the unusual phenomenon of the disappearance of staphylococcal colonies around the mould.

From *Nature* 16 April 1955.