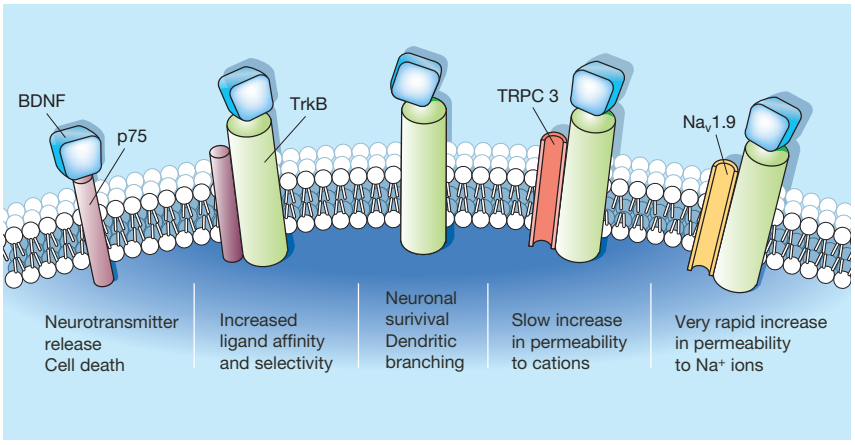

Figure 1 **Brain-derived neurotrophic factor (BDNF) is a versatile protein. There are two receptors for BDNF on the surface of neurons: the neurotrophin receptor p75, which binds all neurotrophins, and TrkB. Each receptor alone binds BDNF with nanomolar affinity, but when they associate, the affinity and selectivity of TrkB for BDNF increase. TrkB can also associate with two different ion channels. TRPC3 is a non-selective cation channel that needs to be phosphorylated by TrkB to open; this is a slow process (acting in the range of minutes). $Na_v1.9$ is selective for Na^+ ions and, as Konnerth and colleagues[1] show, opens within milliseconds following the binding of BDNF to TrkB. The figure also shows some of the functional outcomes of the activation of the BDNF receptors.**

timescale as a voltage change raises several questions. The $Na_v1.9$ channel is best known for its presence in small sensory neurons of the dorsal-root and trigeminal ganglia[6], where, together with $Na_v1.8$, it may play a key part in the physiology of neurons involved in pain perception[6,7]. The expression of $Na_v1.9$ is regulated by another growth factor, glial-cell-derived neurotrophic factor (GDNF). These sensory neurons do not express TrkB, so it will be interesting to see whether one component of the GDNF receptor, the tyrosine kinase Ret, is also associated with $Na_v1.9$, and whether GDNF causes rapid changes in membrane potential. If so, this could have implications for our understanding of pain sensing.

In a similar vein, most $Na_v1.8$-expressing and many $Na_v1.9$-expressing neurons also express TrkA[7] — the tyrosine kinase receptor for nerve growth factor (NGF). NGF has been associated with pain sensing in many ways[8], and one wonders whether it may trigger the rapid opening of $Na_v1.8$ or $Na_v1.9$ via TrkA.

Another question is whether the BDNF-induced, TrkB-mediated depolarization seen in all neurons of the central nervous system (CNS) tested so far can be attributed to $Na_v1.9$. Although Konnerth and colleagues' latest report[1] indicates that $Na_v1.9$ is expressed by hippocampal CNS neurons, the levels of expression are probably much lower than those in sensory neurons[6]. Finally, it has not yet been demonstrated biochemically that TrkB associates directly with $Na_v1.9$, although TrkB does associate with other transmembrane proteins[3,9], such as the neurotrophin receptor p75 and the nonspecific cation channel TRPC3 (Fig. 1).

Intriguingly, the binding of BDNF to TrkB also increased the permeability of the TRPC3 channel[9], although this required the enzymatic activity of TrkB and was considerably slower (minutes instead of milliseconds).

Thus, one of the last remaining distinctions between the physiological properties of neurotrophins and neurotransmitters seems to have disappeared. Work on neurotransmitters may become a source of inspiration for researchers interested in the neurophysiology of neurotrophic factors, and one of the next questions may be how the effects of BDNF on ion channels are rapidly inactivated. Mechanisms involving receptor internalization might be too slow to eliminate this poorly diffusible protein, which is also fairly resistant to protein-degrading enzymes. But BDNF-induced desensitization, as occurs with neurotransmitter receptors, may be an attractive possibility to explore. ■

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100 YEARS AGO

The question I wish to bring to your notice to-day is an old one: if two events happen simultaneously or one follows the other at a short interval of time, does this give us any reason to suppose that these two events are connected with each other, both being due to the same cause, or one being the cause of the other? Everyone admits that the simple concurrence of events proves nothing, but if the same combination recurs sufficiently often we may reasonably conclude that there is a real connection. The question to be decided in each case is what is "sufficient" and what is "reasonable". Here we must draw a distinction between experiment and observation. … The cause of the difference lies in the fact that in an experiment we can control to a great extent all the circumstances on which the result depends, and we are generally right in assuming that an experiment which gives a certain result on three successive days will do so always. But even this sometimes depends on the fact that the apparatus is not disturbed, and that the housemaid has not come in to dust the room. Here lies the difference.
From *Nature* 16 October 1902.

50 YEARS AGO

Our present political systems are likely to be modified. Democracy lacks survival value. The state of parasitism on the community engendered by modern social conditions is impermanent because in the end the parasite destroys its host and then itself perishes: the process is likely to be hastened by the concomitant reduction of the more intelligent, these being now driven to have few or no children. It will be the non-parasitic communities that will survive, and those that multiply most will dominate the earth by sheer numbers. For this reason the author thinks that world agreement to control population could never be attained: an aggressor nation or bloc would never permit their people to restrict their numbers, and other nations that wished to survive would have to follow suit. Government would possibly be by some "hero" who has sufficient sense to adapt himself to a society of dense population. Here intellect will count, but morality may not, since "in a highly competitive world, the sinner has many advantages over the saint".
From *Nature* 18 October 1952.