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## 50 YEARS AGO

A striking picture of the dangers which confront men of science has been prepared recently by Gerard Piel... At the outbreak of the Second World War, he writes, science was a kind of ideal world republic. The scientific community was an international community. It was the only truly international community at an epoch that was to see nationalism and the narrower concerns of national power rise again to ascendancy in world politics. Statesmen discovered early in the War that science is an essential element of national strength... Accordingly, each major power has sought to monopolize the talents of its scientists and to put them to work in the name of national security. This suppression of international motives in favour of national ends has now had serious consequences upon the life of science... Scientists are agreed, in the first place, that there has been a dangerous diversion of resources and talent from the really significant long-range concerns of science to the narrower short-range objectives of practical results.

From *Nature* 17 December 1955.

## 100 YEARS AGO

The report of the chief of the United States Weather Bureau for the fiscal year 1903–4 contains... an interesting account of the very useful operations of that organisation. Weather forecasts for thirty-six and forty-eight hours in advance are issued for each State, besides special warnings of gales, cold waves, floods, &c. To mention one case only of the utility of storm warnings — a hurricane which advanced from the West Indies destroyed property to the value of 100,000 dollars during its progress over Florida, but, owing to timely notice, comparatively little damage was done to vessels, as they remained in port in consequence of the warnings. Prof. W. L. Moore reiterates the hope that the time will come when it will be possible to forecast the weather for coming seasons, but that time has not yet arrived.

From *Nature* 14 December 1905.

50 & 100 YEARS AGO

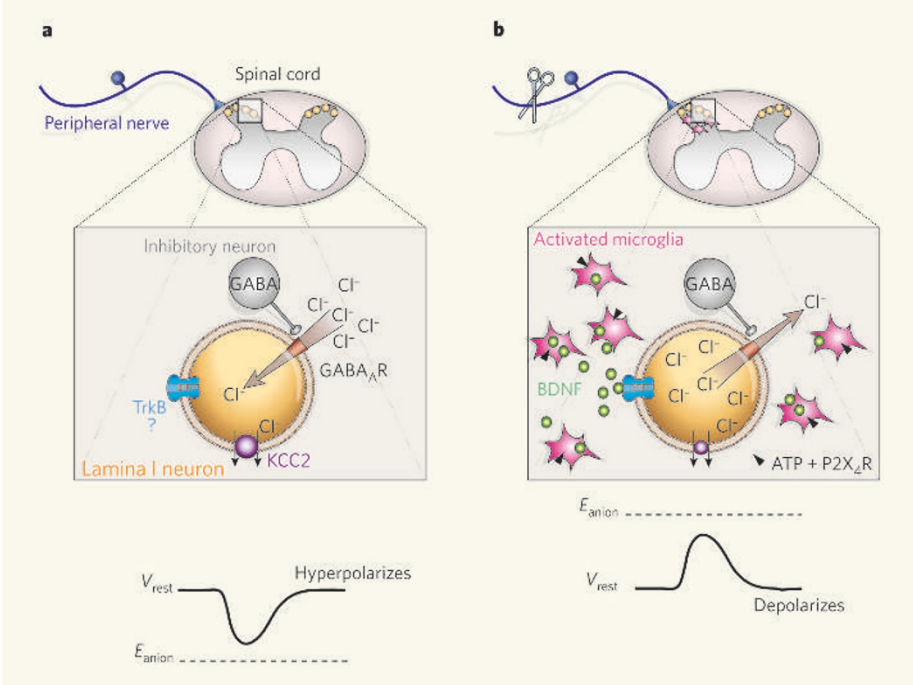


**Figure 1 | A pathway of pain.** Coull and colleagues[3] reveal that microglial–neuronal signalling mediated by BDNF disrupts inhibition of rat lamina I spinal-cord neurons and maintains neuropathic pain. **a**, Activation of $GABA_A$ receptors ($GABA_AR$) normally leads to an influx of anions (principally chloride, $Cl^-$), causing hyperpolarization (inhibition), because the potential at which the anion flux switches from inward to outward ($E_{anion}$) is negative with respect to the resting membrane potential of the neuron ($V_{rest}$). **b**, Following peripheral nerve injury, activated microglia (with ATP-stimulated $P2X_4$ receptors) release BDNF, which acts on the TrkB receptor to modify $E_{anion}$, probably by reducing levels of the potassium-chloride co-transporter KCC2. As $E_{anion}$ is now positive with respect to $V_{rest}$, $GABA_A$-receptor activation leads to an efflux of anions, depolarizing the lamina I neurons. Blockade of this microglial–neuronal signalling pathway alleviates chronic neuropathic pain in the rat model.

potential. $GABA_A$-receptor activation then results in anions flooding out of the neuron, making the neuron's membrane potential more positive, or depolarized, relative to the resting membrane potential (Fig. 1b)[4]. As a result, the normally inhibitory transmitters GABA and glycine are no longer able to suppress signalling in the lamina I pain pathway.

In the latest study[3], Coull and colleagues investigated whether the activation of microglia following nerve injury is responsible for this switch in the effects of glycine and GABA. Increased synthesis and activation of the ATP receptor $P2X_4$ found on microglia are required for the development of allodynia following nerve injury[2]. The authors therefore stimulated microglia with ATP and applied them to the spinal cord of rats. The animals developed allodynia, as assessed by paw withdrawal from a light mechanical stimulus. Electrophysiological recordings in spinal-cord slices taken from these allodynic animals showed that ATP-stimulated microglia positively shifted the $E_{anion}$ in lamina I neurons and rendered GABA effects depolarizing, rather than hyperpolarizing, in these neurons.

How do activated microglia communicate with lamina I neurons? To answer this question, Coull *et al.* examined the effects of BDNF, as this protein is secreted by microglia[6], is involved in chronic pain[7] and can cause shifts in anion gradients in the brain[8]. The authors found that spinally administered BDNF produced allodynia and induced the predicted change in the anion gradient, enabling GABA to depolarize the lamina I neurons rather than inhibit them. In a rat model of nerve injury, blocking the spinal action of BDNF on its receptor, TrkB, reversed an established allodynia, confirming that BDNF is actually released in the spinal cord and is required for the development of neuropathic pain. Furthermore, when BDNF–TrkB signalling was prevented, spinal slices from nerve-damaged animals did not show the typical depolarizing shift in $E_{anion}$.

Coull *et al.* then confirmed that microglia are indeed the source of the BDNF, which until now was thought to be released from neurons during pain processing. They showed that ATP-stimulated microglia were unable to produce allodynia or shift $E_{anion}$ when spinal BDNF–TrkB signalling was blocked. The authors also created microglia that could not synthesize BDNF, and showed that, although these microglia have otherwise normal ATP responses, they did not release BDNF when stimulated with ATP. Significantly, these BDNF-deficient microglia did not cause allodynia or shift $E_{anion}$ when administered spinally.

This work firmly establishes BDNF as a crucial mediator of microglial–neuronal signalling during neuropathic pain. Furthermore, it highlights several remaining questions. Where does the ATP that stimulates