Pharmacology

Substance P equals pain substance?

Leslie Iversen

Since von Euler and Gaddum first described substance P (SP) more than 60 years ago[1], much evidence has accumulated to suggest that this undecapeptide is released from the terminals of certain sensory nerves, as a chemical neurotransmitter or modulator[2]. The sensory function of SP is thought, from more circumstantial evidence, to be related to the transmission of pain information into the central nervous system (CNS)[2,3]. This idea is now supported by two studies reported by Cao *et al.*[4] and De Felipe *et al.*[5] on pages 390 and 394, respectively, of this issue. Both groups find that when the function of SP is genetically disrupted in mice, the animals show reduced responses to painful stimuli.

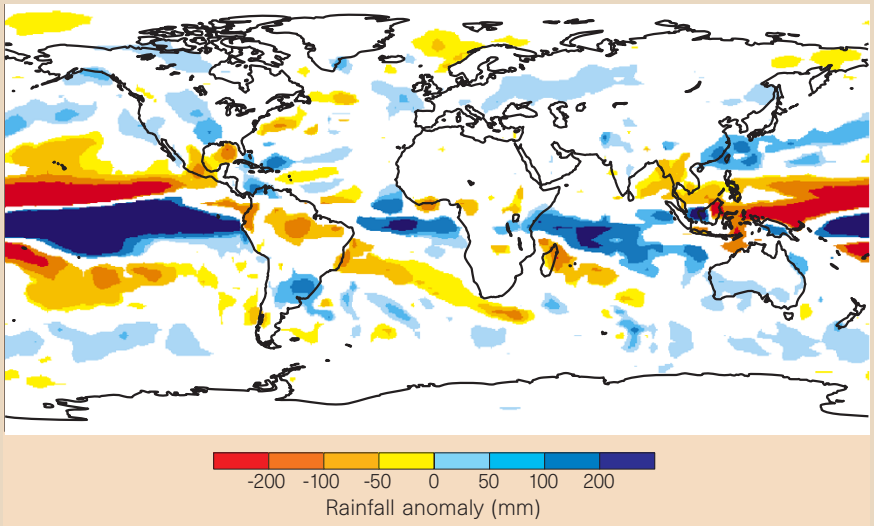
Cao *et al.*[4] studied mice in which the preprotachykinin A gene was disrupted. This gene encodes the precursor from which both SP and the closely related neuropeptide neurokinin A (NKA) are made. As expected, the mice lacked any detectable SP or NKA, although their development, ability to reproduce and behaviour were unaffected. The animals also showed normal thresholds for reactions to various painful stimuli, such as heat, mechanical pressure or chemical irritants. But when the intensity of the painful stimulus was increased, the knockout mice showed blunted responses, evidenced by increased latencies in the response to the stimulus. The importance of SP/NKA seemed to apply only to a certain 'window' of pain intensities — when the intensity of the pain stimulus was further increased, the responses of the knockout animals did not differ much from those of the wild-type mice.

De Felipe *et al.*[5] studied a strain of mouse that lacked the neurokinin-1 (NK-1) receptor, with which SP interacts. These animals resembled those studied by Cao and colleagues in several respects: they did not show any changes in acute pain thresholds in mechanical, electrical or noxious heat tests, but their responses were blunted in tests that involved more intense noxious stimuli. When sensory nerves are subjected to an intense period of noxious stimulation, normal animals show a 'wind-up' phenomenon, whereby spinal reflexes are temporarily increased. This is thought to reflect the sensitization of CNS mechanisms by intense noxious stimulation. But such a wind-up was completely absent in the NK-1-receptor knockout mice.

As well as acting in the CNS, SP and other sensory neuropeptides can be released from the peripheral terminals of sensory nerve fibres in the skin, muscle and joints. This release is thought to be involved in 'neurogenic inflammation' — a local inflammatory response to certain types of injury or infection[6]. But the authors found that this process was impaired in both types of

Climate forecasting

Outlook – probably wet in parts



Weather is too chaotic to be predicted more than ten days or so ahead. So why should we believe the global rainfall forecast, pictured here, made a few months in advance?

Well, this isn't really a weather forecast, in which the evolution of individual weather systems is predicted. It is a climate forecast, described elsewhere in this issue (Stockdale, T. N., Anderson, D. L. T., Alves, J. O. S. & Balmaseda, M. A. *Nature* 392, 370–373; 1998), which uses a global model of the coupled oceanic and atmospheric circulations to calculate the statistical behaviour of large-scale weather patterns and the main physical influences on those statistics. The model calculates not only the mean (predictable) shift in climate for a season, but also estimates the random (unpredictable) component. Forecasts are therefore expressed as probabilities. For example, the model predicts that it is about 70% certain that southeast China will continue to experience the unusually wet weather it has been suffering of late.

The forecast was completed at the end of January 1998, and the map shows predicted total rainfall anomalies for this year's March–April–May season, relative to long-term mean rainfall for the same season; blue is wet, red is dry. Uncoloured areas represent a low-confidence forecast. As well as southeast China, the central United States and western central Eurasia are predicted to be unseasonally rainy, whereas the forecast is that central Mexico and Indo-China will undergo shifts to an unusually dry season. Although some of these predictions are perhaps not so surprising in the wake of the present El Niño, Australia — which would normally suffer drought after an El Niño — seems to be in for a relatively wet time.

The high rainfall that contributed to last summer's severe and unexpected floods in central Europe was predicted using this approach. But a successful rainfall prediction is not necessarily a sign of a reliable forecasting system. On the one hand, a forecast is only a probabilistic statement (so a good forecast might get the rainfall wrong); on the other, the model might forecast the correct rainfall for the wrong reasons. The European Centre for Medium-Range Weather Forecasts, where the map was produced, is investing substantial resources in addressing this 'verification' issue, largely by using past datasets to increase model confidence, and is now in a quasi-operational forecast phase. Go and look at the up-to-date seasonal forecasts (http://www.ecmwf.int), but don't bet your house on them.

Philip Newton

knockout animal. Moreover, the response to capsaicin was also absent or considerably reduced in the knockout mice. Normally, when this irritant is administered to the skin of the ear, it evokes a local oedema (accumulation of fluid) by provoking a release of sensory neuropeptides[7].

Similar impairments of the neurogenic inflammatory response to capsaicin and the inflammatory response in the lung after administering an immune complex have already been reported in NK-1-receptor knockout mice by Bozic *et al.*[8]. On the other hand, the knockout animals studied by Cao *et al.* and De Felipe *et al.* responded normally to an inflammatory stimulus that did not involve a neurogenic component (the injection of complete Freund's adjuvant into a hind paw). Both the local inflammation and the delayed development of heightened pain sensitivity after these injections were unimpaired.

These new data come at an important time. Several pharmaceutical companies are developing drugs that act as potent antagonists of NK-1 receptors, although early results with such agents in animal tests of pain have often proved difficult to interpret. This is partly because the functional roles of SP and the NK-1 receptor are complex, and partly because some of the initial SP antagonists could not adequately penetrate the CNS or had other pharmacological activities that confused the results[9]. Nevertheless, the results with NK-1 antagonists mirror the present findings quite well — the drugs do not alter acute pain thresholds, but they do affect responses that involve more intense noxious stimulation. For example, they block the wind-up of spinal reflexes[9–11].

The results with the knockout mice and with the new SP antagonists show that SP is only one of the many complex mechanisms involved in pain perception. Mild and severe forms of pain involve other neurochemical mechanisms, among which L-glutamate is clearly important[12]. De Felipe *et al.*[5] also report that, in the NK-1-receptor knockout mice, the analgesic response to cold-water swim stress was considerably impaired. Moreover, these animals were much more aggressive than wild-type mice. The authors conclude "… that SP is important for orchestrating the response of the animal to major stressors such as pain, injury or invasion of territory". If they are right, then SP-receptor antagonists may have broad therapeutic applications in the treatment of a variety of stress-related illnesses, in addition to their potential as analgesics. □

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Palaeoclimatology

Icing the North Atlantic

Richard B. Alley

The North Atlantic region has experienced large, abrupt climate changes in the past[1], and similar changes occur in some models of the future[2]. But there is disagreement as to whether these changes originate in the North Atlantic itself or are transmitted to the region from elsewhere. In their paper on page 373 of this issue[3], McCabe and Clark tackle the question with new data on the extent and movement of the British Ice Sheet, which covered an area around the northern Irish Sea towards the end of the last ice age. From these data, they argue that the advance and retreat of one of the great ice sheets feeding the North Atlantic, the Laurentide, probably caused some of the big climate jumps of the past.

Two related oscillations are especially prominent in North Atlantic palaeoclimatic records — the lower-frequency Bond and the higher-frequency Dansgaard–Oeschger cycles (Fig. 1). Because signals of Dansgaard–Oeschger and, especially, Bond oscillations were recorded in geographically diverse areas extending well south of the Equator[4], they should offer important clues in understanding and predicting climate changes.

In the Dansgaard–Oeschger cycle, rapid jumps (sometimes within less than ten years) of up to one-half of the glacial–interglacial amplitude in temperature and other climate variables occurred between climate states. Cold, dry and windy atmospheric conditions around the North Atlantic occurred when the ocean's surface waters were fresh and cold[1]. Progressive cooling through several such Dansgaard–Oeschger cycles, followed by an especially abrupt warming, defines the Bond cycle. The coldest part of each Bond cycle in North Atlantic cores is marked by a so-called Heinrich layer rich in debris transported by icebergs[1] (Fig. 1).

These Heinrich layers thicken towards Hudson Bay, and the thicker parts were deposited anomalously rapidly. Ice-rafted debris in the thin marginal regions of Heinrich layers and between them has many sources from around the North Atlantic, but the thicker parts of Heinrich layers are dominated by material from Hudson Bay[5–8].

Many models for these oscillations invoke processes taking place in ice sheets and the North Atlantic Ocean. Today, in an interglacial, cold and salty waters of the North Atlantic are dense enough to sink into the deep ocean, from where they flow south and are balanced by northwards surface flow from the tropics. Increased supply of fresh water in the north could dilute the northern surface waters sufficiently to prevent them sinking. Loss of the balancing, warm surface flow would cause high-latitude cooling and associated climate changes[9], until salt build-up in the ocean or reduced freshwater supply reinitiated North Atlantic Deep Water formation. Forced or internally generated changes in freshwater delivery, possibly including warming-enhanced ice melt or precipitation, would create the observed

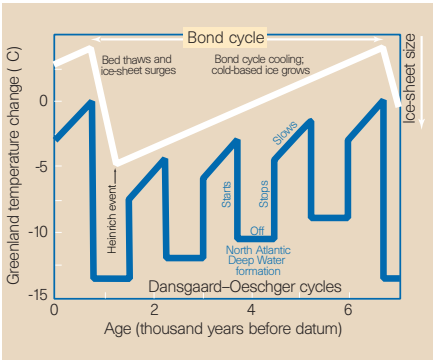

Figure 1 **An idealized climate cycle in the North Atlantic region, assuming North-Atlantic-centred models for oscillating North Atlantic Deep Water formation[10] and surging of the Laurentide Ice Sheet[11]; time and temperature scales are approximate. The 1,500-year Dansgaard–Oeschger oscillations are related to weakening and shutdown of deep water formation as ice melt or other processes dilute the North Atlantic, and then resumption of deep water formation in response to the build-up of salt. The longer-term cooling of the Bond cycle is related to the downwind effects of the growing Laurentide Ice Sheet that covered Hudson Bay, and is terminated by a surge that thins the ice. Successive Bond cycles show warming or cooling in response to orbitally modulated ice-age cycles, and their coldest part is marked by a Heinrich layer. These are deposits in North Atlantic cores that consist of ice-rafted debris largely originating from the Hudson Bay area.**