So, does this rather mundane explanation mean we have to discard our view of Stonehenge as an ancient temple in exchange for one of an elaborate livestock control system? Probably not. There may still have been elements of ritual behaviour at the Milfield site. The Neolithic inhabitants of the basin lived in small groups, probably with their own agricultural plots. Certainly, the presence of 'inscribed grazing areas'[5] (defined areas of upland containing clear concentrations of cup and ring engravings) suggests that different communities may have claimed areas of pasture as their own. The Coupland enclosure in the valley, on the other hand, is likely to have been a neutral zone, and there is no reason why people should not have met here to exchange commodities as well as to over-winter their cattle. Perhaps the very coming together of different groups in one special area designated it as sacred ground, and led to later ritualistic use of the enclosure. It could have been a focus for activities such as the feasts suggested to have occurred at causewayed camps in southern Britain[6].

If we suppose that events such as markets, feasts and the kraaling of cattle took place at certain set times of the year, the Coupland enclosure is perhaps not so far removed from Stonehenge after all, where seasonal astronomical events were clearly of great importance. Although there is no evidence at the Coupland site for a circle monument inside the henge (wood, stone or otherwise), the architectural antecedents for the henge tradition — outer bank and internal ditch — may have their roots in this and other, as yet undiscovered, sites. □

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Circadian rhythms

Time to get excited by GABA

Christopher S. Colwell

Much of the inhibitory synaptic transmission that occurs in the brain is thought to be mediated by γ-aminobutyric acid (GABA). Synaptically released GABA activates $GABA_A$ receptors, leading to the opening of chloride-permeable ion channels. The resulting hyperpolarization (as well as the underlying increase in conductance) inhibits the electrical activity of the neuron, making it less responsive to excitatory input. This model is so well accepted as the basis for fast inhibitory synaptic transmission that the mere presence of the enzyme that is responsible for making GABA is usually enough to label a particular pathway as being inhibitory.

But there is now evidence that GABA can also act as an excitatory transmitter. On page 598 of this issue, Wagner and co-workers[1] report that mature neurons in the suprachiasmatic nucleus (SCN) of the hypothalamus can be excited by GABA, through a $GABA_A$-dependent mechanism. Cells in the SCN are responsible for the generation of circadian rhythms in mammals, undergoing spontaneous changes in their electrical properties between day and night. Interestingly, the effect of GABA also seems to show diurnal variations — the excitatory response is seen only during the day. So, at least for SCN neurons, the time of day determines whether GABA acts as an inhibitory or an excitatory transmitter.

What mechanisms are responsible for this daily change in the action of GABA? Because $GABA_A$-gated channels are selectively permeable to chloride ions, the GABA equilibrium potential is largely determined by the chloride equilibrium potential. The GABA equilibrium potential is the membrane potential at which no net current will flow, and the membrane will tend to move to this potential after the application of GABA. In the model proposed by Wagner *et al.*[1], SCN cells show a daily rhythm in the GABA equilibrium potential such that, during the day, it is several millivolts positive relative to the resting membrane potential (Fig. 1). Accordingly, during the day, when GABA opens the chloride ion channel, the membrane potential becomes more positive and action potentials are generated.

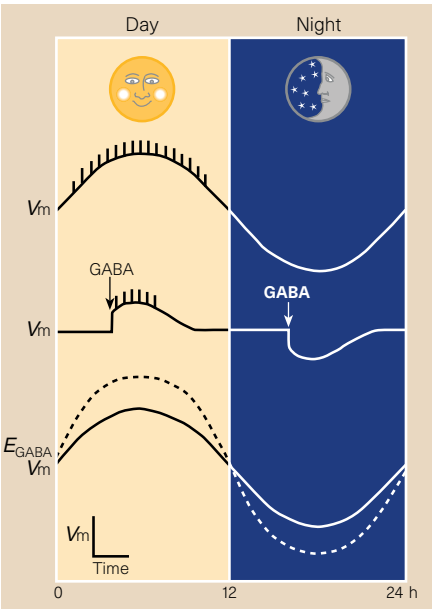

Figure 1 **The neurotransmitter γ-aminobutyric acid (GABA) can be either excitatory or inhibitory in cells of the suprachiasmatic nucleus (SCN). These cells are responsible for the generation of circadian rhythms in mammals, and undergo spontaneous changes in their electrical properties (V_m) between day and night. Wagner *et al.*[1] now report that the effect of GABA on these cells also varies with the time of day, because GABA produces an excitatory response during the day, but not during the night. The underlying mechanism seems to be a daily shift in the GABA equilibrium potential (E_{GABA}) from being depolarized relative to the resting membrane potential during the day, to being relatively hyperpolarized during the night. Daily changes in intracellular chloride concentration are thought to drive this switch from GABA-mediated excitation to inhibition.**

The opposite happens during the night, because the GABA equilibrium potential is negative relative to the resting membrane potential. So GABA acts as an inhibitory neurotransmitter, decreasing the number of action potentials that are generated. The most likely explanation for these fluctuations in the GABA equilibrium potential is, perhaps, a diurnal change in the intracellular concentration of chloride. Unfortunately, it has proven technically difficult to measure the GABA equilibrium potential of SCN cells without altering the internal chloride concentration.

Although it is not yet clear how common the action of GABA as an excitatory transmitter may be, there is a precedent for time-dependent changes in its effects. For example, in the developing nervous system, it is well established that GABA can excite cells[2]. The mechanism seems to be an elevation in the levels of intracellular chloride in immature neurons. So activation of $GABA_A$ receptors would elicit a depolarizing current, and GABA could function as an excitatory transmitter. But, in these cases, the excitatory effect of GABA becomes inhibitory as the neurons mature.

In another example, large amounts of exogenous GABA or the high-frequency activation of inhibitory synapses produce a biphasic response in the brain of mature animals[3]: initial hyperpolarization is followed by an overshoot to depolarizing and action-potential-generating potentials. So there seem to be a growing number of situations in which it is appropriate to think of GABA as being a transmitter that can be excitatory or inhibitory, depending on the physiological conditions.

The observation by Wagner *et al.*[1] — that basic properties of synaptic transmission

could vary with the time of day — is fundamentally important. Most organisms, including humans, show daily rhythms in their physiology and behaviour. Although most of these rhythms are seen at the level of the output of a physiological system, the new study shows that even the most basic property of cell–cell communication in the nervous system (that is, whether the release of transmitter excites or inhibits the postsynaptic cell) can also vary with the circadian cycle. Add to this observations that the properties of a cellular membrane, its second-messenger systems and its transcriptional/translational machinery can all be rhythmically regulated[4,5], and the emerging view is that even the most basic cellular and molecular properties of a cell can be subject to circadian regulation.

What does the work by Wagner *et al.*[1] mean for our understanding of the circadian rhythms that are generated by cells in the SCN? Most of these neurons send out processes containing GABA, which form synapses with other cells in the SCN. We now have to consider the possibility that these cells switch from being excitatory to inhibitory interneurons, depending on the time of day. So is this switch responsible for generating the daily rhythm in spontaneous neural activity that is characteristic of SCN cells? Probably not, as there is evidence to suggest that this rhythm is generated by intracellular processes that do not depend on synaptic communication[6]. But the switch in sign may boost the amplitude of the neural rhythm, and be involved in driving the outputs from the SCN.

Agonists towards GABA can have an impact on the circadian system[7], so there is every reason to think that understanding the physiological role of GABA-mediated synaptic transmission in the SCN will help to explain circadian phenomena in mammals. The findings of Wagner *et al.* also force us to re-evaluate our thinking about GABA as a signalling molecule — they raise the possibility that under certain physiological conditions, or at certain times, GABA can act as an excitatory transmitter. Certainly, for SCN cells, there are times to be excited by GABA. □

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Biosensors

Switching channels makes sense

Anthony P. F. Turner

The Atlas moth can follow a thinly laid trail of single molecules. Can we mimic it? Building a device to do that, and so pass the sternest test of sensitivity, is one of the ultimate goals of the biosensor technologist. Pursuit of this prize is likely to lead to considerable commercial benefit from the production of highly sensitive diagnostics, and exciting possibilities for computers that use biochemicals in place of conventional solid-state electronics. On page 580 of this issue[1] Cornell *et al.* describe an important step forward — a stable lipid membrane that can act as an ion gate, opened or closed by the binding of single molecules.

Over the past decade, biosensors (sensors incorporating a biological or biologically derived sensing element[2]) have achieved considerable commercial success, with current worldwide sales of over half a billion US dollars a year. The field has been dominated by enzyme-based biosensors, and in particular by disposable enzyme electrodes for home blood-glucose measurement[3]. Immunodiagnostics and other affinity systems have so far been relatively unaffected by this emerging technology, with consumer products focusing on immunochromatographic approaches such as the new test strips for pregnancy and fertility.

Biosensor technology has had a smaller but significant impact on affinity assays performed in the laboratory, especially in the pharmaceutical industry. Several companies sell real-time bioaffinity assays based on measuring the change in refractive index resulting from antibody–antigen interactions at a sensing surface. The best known of these exploit surface plasmon resonance (oscillations of electrons in a thin metal layer) at an optical interface to measure affinity reactions occurring in a thin polymer matrix coating[4]. Many companies are working to miniaturize this and related technologies, in an attempt to produce a hand-held immunosensor that might be similar in both cost and size to the pocket-sized glucose biosensors already on the market. Such instruments could be used for home testing or for non-medical applications such as environmental or food monitoring. Target analytes include toxins, allergens, disease markers, hormones, bacteria, viruses, antibodies, DNA, drugs and pesticides.

The idea of mimicking nature by harnessing an affinity reaction to open a gate or switch in a membrane is not new. Various ion-channel sensors were described in the late 1980s, and by 1989 there remained three

100 YEARS AGO

In connection with the recent correspondence in these columns on luminous phenomena observed on mountains, it is interesting to direct attention to a very remarkable series of observations of electrical storms on Pike's Peak, Colorado, contained in vol. xxii. of the Annals of the Astronomical Observatory of Harvard College, and described in NATURE... . Luminous jets appeared very often along the telegraph wires for the length of an eighth of a mile, and the anemometer cups looked like revolving balls of fire. Upon touching the anemometer under these conditions, an observer found "his hands instantly become aflame. On raising them and spreading his fingers, each of them became tipped with one or more cones of light nearly three inches in length."
From *Nature* 3 June 1897.

50 YEARS AGO

Prof. J. Kaplan proposes the name 'active oxygen' for certain luminous phenomena observed by him "just as the name active nitrogen was given to similar phenomena in nitrogen". I write to point out that this is not historically correct. ... The chemical activity referred to was the combination with metals such as sodium and mercury, to form nitrides, and with organic materials to form cyanogen compounds. Striking luminous phenomena often accompany these chemical actions, but it is wrong to regard these effects as the essence of the matter. As a matter of fact, the number of nitrogen molecules which emit a photon of afterglow light is very small compared with the number which become chemically active. For this reason, I do not think that the afterglow should be regarded as the essential phenomenon of active nitrogen, and I do not think that in the present state of knowledge the term 'active oxygen' should be applied by analogy, when only luminous phenomena are so far known to be involved. This would only cause confusion.
From *Nature* 7 June 1947.

Many more abstracts like these can be found in *A Bedside Nature: Genius and Eccentricity in Science, 1869–1953*, a 266-page book edited by Walter Gratzer. Contact David Plant (e-mail: subscriptions@nature.com).