than concentration data, representative sampling of poorly mixed reservoirs is hard to achieve or evaluate. However, combining isotope and concentration data into a three-dimensional picture may provide an invaluable tool for revealing and evaluating sampling biases and systematic errors. Surprisingly, Kim and Craig have not presented the concentration dimension of their data set.

A rigorous isotope balance may also require abandoning the assumption that only sources matter. Although N_2O probably enters the stratosphere without altering its isotope signature[2], its signature is certainly changed there by reactions with oxygen atoms and, in a different way, by photolysis. Hence any return flux to the troposphere of stratospheric air containing altered N_2O may enter into the isotopic book keeping. We know that some air from N_2O-depleted levels in the stratosphere returns by such mechanisms as tropopause folding, subsidence in polar vortices, and other large-scale processes. Ronald Prinn, an atmospheric dynamicist working with global N_2O distributions, confirms that the recirculation flux cannot simply be assumed trivial (personal communication). Cicerone also emphasized[1] that some soil regions are N_2O sinks needing further evaluation; their effects on isotope ratios should be included. □

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NEUROBIOLOGY

A depression long awaited

Charles F. Stevens

ARTOLA, Bröcher and Singer provide, on page 69 of this issue[1], the first confirmation of a result[2] that has been the source of a silent controversy in neurobiology over the past year. They describe the conditions under which the strength of a synapse between two neurons is reduced with use and thereby support the earlier finding of this phenomenon, long-term depression, as the obverse face of the long-term potentiation coin.

Long-term potentiation (LTP), is widely accepted as a neuronal substrate for learning and memory. Because forgetting is such a conspicuous counterpart to learning, one might expect to find the cellular analogue of forgetting as an inverse of LTP: neuronal forgetfulness might be an enduring decrease in synaptic strength that follows the heavy use of a specific synapse.

Under what circumstances could such long-term depression (LTD) occur? LTP results when the repeated use of one of a neuron's synapses is correlated with the activity of another. Stanton and Sejnowski[2] thus reasoned that an anticorrelation between the activities of the synapses should favour LTD, the inverse of LTP. They designed an experiment in which they sustained a constant level of use of the synapse while switching between situations in which its activity was correlated and anticorrelated with that at other inputs. LTP occurred when synaptic activity was correlated, and this increase in synaptic strength could be reversed when activities were negatively correlated. Although Stanton and Sejnowski did not analyse the mechanism of LTD fully, they suspected nevertheless that the voltage of a neuron is involved and noted that the phenomenon was found only when the neuron was prevented from depolarizing during stimulation of its excitatory inputs. Of course, it was already known that LTP develops through synaptic use when the neuron is sufficiently depolarized to allow influx of calcium ions through NMDA-receptor channels at its activated synapses.

This all makes great sense, but the problem remains that the precise conditions for producing LTD are not well defined, and three respected groups have been unable to find LTD using what they believed to be the conditions reported by Stanton and Sejnowski. The controversy, then, involves the very existence of LTD. Sceptics suspect that the original report involved some sort of artefact, although no one has suggested a convincing one, whereas others accept the existence of LTD and feel that the failure to confirm the original observations means that the correct procedures were not followed. The controversy has been rather muted because of a reluctance, and sometimes inability, to publish negative results.

A certain amount of confusion has been added to the controversy because, in the still-maturing field of synaptic plasticity, different phenomena have been given the same name. Several distinct types of LTP have been described which appear to have little in common at the mechanistic level. And a kind of LTD[3–5] — interesting and important but quite different from the LTD under discussion — has been studied at particular synapses in the cerebellum and parts of the hippocampus.

Singer's group has not only found LTD as the inverse of LTP, but has also proposed a specific idea about the necessary conditions for obtaining it. According to their observations, LTD occurs when a neuron is depolarized, but not sufficiently for it to reach the threshold for calcium influx through the NMDA receptor channels. Thus neurons have a narrow window of voltages at which LTD will be produced when the synapse is used: near resting potential and below, the use of a synapse does not alter its strength; above a depolarization of perhaps 20 mV, LTP develops; but between resting potential and the LTP threshold, LTD develops and the increase of synaptic strength produced beforehand by LTP is reversed.

The experiments were done not in the hippocampus — that old standby preparation for LTP — but rather in slices from the visual cortex. And the membrane potential was regulated during synaptic use not by directly passing a current through the recording electrode, but by altering the dose of bicuculline, a drug that blocks activity at inhibitory synapses and thus permits the neuron to be more or less depolarized (according to the dose) by antagonizing the inhibitory activity that attends the stimulation used. With no bicuculline, neither LTD nor LTP was found; with small doses, LTD was observed; and with doses that blocked most of the inhibitory synaptic activity, LTP followed synaptic use. Carefully done as the new experiments are, they probably will not end the silent controversy over LTD, because some loose ends remain.

The results show that LTD can be produced if a synapse is used while the neuron's voltage is within a remarkably narrow window. If the neuron is hyperpolarized, synaptic strength is unaffected; if it is depolarized by more than about 10 mV, LTP results; in between, synaptic use causes LTD. For example, Goldman *et al.*[6] failed to find LTD when synapses were used heavily in the presence of APV, a drug that blocks NMDA receptors. This blockage stops the flow of calcium into the synapse and LTP is not triggered. Under these conditions LTD should occur, according to the simplest interpretation of Singer's hypothesis, but it did not. Thus the controversy continues, but LTD is such an important phenomenon that we can expect a satisfactory resolution in the next year or so. □

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