The new dopamine receptor subtype D_3 cloned by Sokoloff *et al.*[1] may clarify many of these dilemmas and provide powerful new strategies for developing safer, more effective antipsychotic agents. Sokoloff *et al.* screened cDNA and genomic libraries using probes based on the cloning of dopamine D_2 receptors by Civelli and associates[9]. The D_3 receptor displays the seven putative transmembrane-spanning domains characteristics of G-protein-linked receptors and about 50 per cent of its amino acids are the same as those of D_2 receptors. Nevertheless, the drug specificity of D_3 receptors expressed in transfected cells in culture differs in important ways from D_2 receptors, as does the localization of mRNA encoding the two receptor proteins in the brain (see table).

These differences may have substantial clinical relevance. For instance, the dopamine agonists pergolide and quinpirole have therapeutic effects in parkinsonism — actions previously assumed to reflect the stimulation of D_2 receptors. But because these drugs are between 30 and 100 times more potent when interacting with D_3 than D_2 receptors, it is more likely that their therapeutic activities are mediated through D_3 receptors. Their major side-effects are psychotomimetic actions, presumably mediated by dopamine receptors in the limbic regions where D_3 receptors are more concentrated than D_2 sites.

The different locations of D_2 and D_3 receptors may help explain the much greater incidence of extrapyramidal side-effects with butyrophenone neuroleptics such as haloperidol than with atypical neuroleptics such as clozapine and sulpiride. Haloperidol is about 20 times more potent at D_2 than D_3 receptors, whereas the atypical neuroleptics have fairly similar potencies at the two receptors.

Designing novel neuroleptics selective for D_3 receptors may diminish pituitary-related side-effects. By blocking D_2 receptors in the pituitary, classical neuroleptic agents increase the concentration of prolactin in the blood, causing amenorrhea, impotence, and, in some animal studies, an increased incidence of mammary carcinoma. Although there are very high densities of D_2 receptors in the lactotroph cells of the pituitary, they appear devoid of D_3 receptors. Of all the neuroleptics thus far evaluated, none displays more than a fourfold selectivity for D_3 over D_2 receptors. Medicinal chemists should be able to sculpt highly selective D_3 agents free from pituitary side-effects.

The identification of D_3 receptors may clarify some confusing aspects of dopamine research. For instance, ligand binding to the expressed D_3 receptors is not influenced by GTP derivatives, which regulate binding associated with D_2 and D_1 receptors. In the corpus striatum, ligand binding associated with dopamine receptors on intrinsic neurons is regulated by GTP, whereas receptors on terminals of the corticostriate pathway are resistant to GTP[10,11]: conceivably, the corticostriate dopamine receptors are of the D_3 subtype. Indeed, differentiating between the functions of the subdivisions within the corpus striatum may be a particularly notable consequence of the identification of the D_3 receptor.

The dorsal striatum, including the caudate nucleus, is comparatively enriched in D_2 receptors and contains terminals of the nigrostriatal dopamine pathway involved in Parkinson's disease and the extrapyramidal side effects of neuroleptic drugs. The more ventral corpus striatum, selectively enriched in D_3 receptors, includes the olfactory tubercle, islands of Callejae and nucleus accumbens, which are linked to phylogenetically older limbic areas of the prefrontal cerebral cortex, and are the likely sites for antipsychotic drug activity.

In recent years, progress in the search for safer and more effective antipsychotic drugs has been slow, with many workers turning away from dopamine receptors to focus on new sites such as sigma receptors[12]. The discovery of D_3 receptors may rejuvenate research on dopamine, which in the past has given rise to the most important therapeutic agents used in psychiatry and neurology. □

Solomon H. Snyder is at the Johns Hopkins University School of Medicine, 725 North Wolfe Street, Baltimore, Maryland 21205, USA.

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BIOGEOCHEMICAL CYCLING

Bombs and ocean carbon cycles

J. R. Toggweiler

FOR geochemists, the radioactive fallout from the atom bomb tests in the 1950s and early 1960s was a scientific windfall. Studies that tracked the movement of the bomb isotopes out of the atmosphere and into the natural reservoirs of land and sea established an observational basis for the modern view of chemical transport. Thirty years later, the isotopes continue to reveal new facets of the natural world. On page 172 of this issue[1], Druffel and Williams use the penetration of bomb ^{14}C into the organic carbon pools of the ocean to highlight the importance of a large, but poorly understood, reservoir of dissolved organic carbon in the ocean's carbon cycle.

The standard model for the ocean's carbon cycle is built around the gravitational settling of biogenic particles. The sinking particles take carbon from the upper ocean, where CO_2 is fixed by phytoplankton, into the deep sea, where the organic material in the particles is metabolically remineralized or buried in the sediments. The sinking flux, comprising macroscopic biogenic aggregations which include the remains of large phytoplankton, animal tests and animal egesta large enough to sink rapidly[2,3] removes about 10 per cent of the carbon fixed by primary production in the euphotic upper layers of the ocean[4].

The standard model has lately come under seige owing to evidence that the primary pathway for transporting organic material through the water column involves dissolved, not particulate, organic compounds. This viewpoint is based on the recent discovery by Suzuki and Sugimura[5-8] of a large pool of dissolved organic compounds in the upper ocean. The maximum concentration of Suzuki and Sugimura's dissolved organic carbon (DOC), around 300 μM, is found at the surface in the middle latitudes of the ocean. The concentration of DOC decreases with depth in parallel with the disappearance of oxygen, suggesting that the lion's share of the oxygen consumed in the ocean's interior is being used to oxidize dissolved organic matter, not particulate organic material. Analytical difficulties in reproducing Suzuki and Sugimura's results have made it difficult, however, to verify that this characterization of the ocean's carbon cycle is correct.

Druffel and Williams[1] now add new evidence that supports the dissolved organic pathway. They have measured the degree to which the ^{14}C produced by nuclear weapons testing has contaminated the particulate organic carbon (POC) pools, both sinking and suspended, in the North Pacific. At present, inorganic CO_2 in the water below the upper kilometre of the ocean is uncontaminated with respect to bomb ^{14}C. This is not true, however, with respect to the organic carbon in particles. Large settling particles can sink to the bottom in less than a year[2]. Settling particles are also continually 'repackaged'. They break up and are re-formed, and in doing so exchange material with the pool of small particles suspended in the water column. The incorporation of suspended particles into sinking particles is such that the residence time of suspended particles in the deep sea is only 5–10 years[9]. According to the behaviour expected of particles, all the POC now in the ocean, 30 years after the bomb tests, should have $^{14}C/^{12}C$ ratios which are virtually identical to the bomb-contaminated levels observed at the ocean's surface. Druffel and Williams observe that suspended POC below the surface is significantly depleted in ^{14}C with respect to the upper ocean. They argue that the ^{14}C depletion is probably a dilution effect arising from the bacterial uptake of low-^{14}C carbon contained in the DOC pool.

Like the carbon in organic particles, the carbon in the DOC pool acquires a bomb ^{14}C signature when DOC is produced by organisms at the surface. However, the bomb ^{14}C signal reaches the DOC in the interior of the ocean only as fast as the ocean can advect contaminated water into the interior by its relatively slow overturning motions (with a timescale of decades to centuries). Also, the DOC pool is 50–100 times larger than the POC pool and turns over more slowly. Thus, bacteria feeding on DOC incorporate relatively uncontaminated carbon into their cells. As bacteria are eaten and their carbon is incorporated into the tissues of microbial animals, or as bacteria aggregate or otherwise attach themselves onto filterable particles, the low-^{14}C signature of the DOC dilutes the bomb ^{14}C in the particulate pools. The observations of Druffel and Williams thus appear to confirm that a certain fraction of the particulate carbon in the deep sea has reached the deeper levels of the ocean by the dissolved organic pathway.

Measurements of DOC have been made for over 50 years. But according to Suzuki and Sugimura, the older techniques for oxidizing carbon from the DOC pool extract less than half the total pool[6]. The carbon extracted by the older techniques is also very 'old' with respect to ^{14}C (around 6,000 years[10]), and is thus extremely resistant to microbial oxidation. A product of the old-DOC pool size and its ^{14}C turnover rate suggests that the old DOC is produced at a rate which is only 0.25 per cent of the primary production in the ocean[4,10]. Much of the old DOC may come into the ocean via rivers[11].

The extra DOC extracted by Suzuki and Sugimura is concentrated in the thermocline and upper ocean[6]. To maintain an upper-ocean DOC gradient against the tendency of the circulation to reduce it, the biota of the ocean must produce the new DOC in much greater quantities than the old DOC is produced. If one assumes that there is an upper-ocean new-DOC pool of roughly 60 moles m^{-2} (a standing crop equivalent to 120 μM spread over the upper 500 m; ref. 6) and one assumes that the upper-ocean pool is turned over in 20–50 years, then the new DOC must be produced at a rate equivalent to 11–28 per cent of the primary production[4]. Production rates of this magnitude, if valid, attest to a carbon cycle which is dominated by the producers of DOC, whatever they may be[12], and heterotrophic bacteria. As much as three times more carbon may be transported out of the euphotic zone in the dissolved organic form than is transported by sinking particles.

The new DOC must have a ^{14}C age which is similar to that of the inorganic CO_2 in sea water and must be contaminated with bomb ^{14}C, although probably not to the same extent as organic particles. No one has yet succeeded in directly measuring the ^{14}C content of the Suzuki and Sugimura's new DOC. A very powerful statement in support of the dissolved organic pathway in the ocean's carbon cycle awaits proof that the additional DOC extracted by Suzuki and Sugimura contains a much higher $^{14}C/^{12}C$ ratio than the DOC extracted by the old methods. □

J. R. Toggweiler is in the Geophysical Fluid Dynamics Laboratory, Princeton University, PO Box 308, Princeton, New Jersey 08542, USA.

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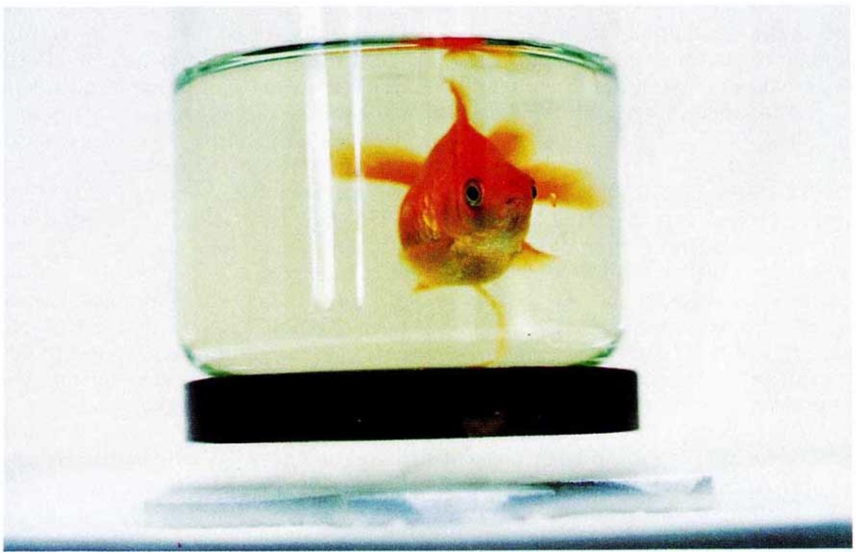
Superconducting boost for goldfish



LEVITATING magnets are a familiar sight in superconductivity research. The cause, the Meissner effect — expulsion of magnetic flux lines from a superconducting material — has long been one of the most dramatic manifestations of the superconducting state. But usually the magnets are rather modest — roughly coin-sized — which explains the interest generated by the picture above when it was presented at a recent meeting* by M. Murakami and colleagues from ISTEC in Tokyo. The 2-kg goldfish bowl is resting on a rare-earth magnet levitated over a liquid-nitrogen-cooled $Y_{1.8}Ba_{2.4}Cu_{3.4}O_x$ (YBCO) superconductor.

The levitation in this example is generated by rather more subtle means than the simple Meissner effect. YBCO belongs to the type II class of superconductors, which permit a degree of penetration by magnetic flux. The flux lines tend to get 'pinned' at defects in the material's lattice. The force holding the bowl up is generated by the resistance to rearrangement of the pinned flux lines, which would result as vertical displacement of the magnet changed the flux density. Its strength is proportional to the sample's critical current and grain size. The advance made by Murakami and colleagues is to prevent cracking of the superconductor's grains by incorporating silver particles in the superconducting matrix: these can absorb mechanical strain without affecting the material's superconducting properties. One hope is that the levitation force may be used to create frictionless bearings, in gyroscopes for example. P.B.

* Workshop on high-temperature superconductivity, University of Cambridge, 13–15 August 1990.