recovery and recycling processes for old lead are becoming a significant source of this metal to the environment.

Lead and silver mining involves three steps: (i) smelting of the lead ore, (ii) purification of the crude lead bullion, and (iii) desilverizing of the lead. At first, operations were crude and often consisted of a pot, a small pit, or simply a heap of rocks on a hillside, arranged so that natural air drafts would stoke the fire. This primitive smeltery—though cheap and versatile—released lead fumes to the air. In ancient times, about 10 to 20% of the lead mined and cupelled was released to the atmosphere (*4*). Improvements in smelting technology reduced the emission factor to 5 to 10% during stage II, and by the mid-19th century (stage III), 2 to 5% of the lead was carried away in the fumes (*11*). From the emission factor, the worldwide flux of anthropogenic lead to the atmosphere is estimated to be 5000 to 10,000 tons per year during the Roman era. Several studies have identified the Roman lead pollution in many parts of Europe, including the snow fields of Greenland (*12*). From about 500 to 1500 A.D., worldwide lead emissions fluctuated between 500 and 1500 tons per year. A steep increase in global lead emissions that began around 1750 A.D. peaked around 400,000 tons per year during 1970 to 1980 and has declined to about 100,000 tons in recent years (*10*). During the last 250 years, emissions of lead have been elevated by a combination of increased industrial demand, large-scale combustion of lead-containing coals, and automobiles. In more recent times, pollution controls have led to a dichotomy—emission rates in the developed countries are going down while those of the developing countries are still increasing (*13*).

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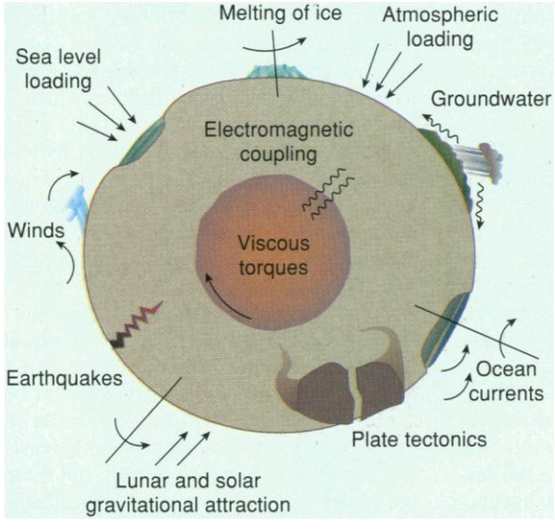
PERSPECTIVES: GEOPHYSICS

Oceanic Effects on Earth's Rotation Rate

Clark R. Wilson

The oceans are vast in extent, fundamentally important to Earth's climate and environment, and difficult to observe. Throughout history, ship-board studies have sampled only a fraction of the ocean's volume, and observations from space, although often global, are limited to properties detectable at the surface. Thus, it is exciting when a fundamentally new observation becomes available, especially one that is global and samples the full depth of the oceans. On page 1656 of this issue, Marcus *et al.* (*1*) report on one such new measure of ocean change—variations in global ocean angular momentum. The new results reflect changes in distribution of mass, which alter the moment of inertia of the oceans on the rotating Earth, and changes in east-west currents, which alter momentum relative to Earth.

Marcus *et al.* estimate ocean angular momentum changes indirectly, using the principle that total angular momentum within the Earth system is conserved (with the exception of changes due to predictable torques applied by the sun and moon). This is the same conservation principle that allows a spinning ice skater to increase angular velocity by redistributing mass (drawing in the arms). The directly measured quantity, therefore, is Earth's rate of rotation, or the corresponding length of the day (LOD), observed in an international effort that relies mainly on the radio astronomy technique of very long baseline interferometry. This method uses radio telescope arrays to determine the speed of rotation and orientation of Earth relative to the reference frame formed by extragalactic radio sources; thus does radio astronomy become an oceanographic science.



As the world turns. Forces (arrows) acting on the solid Earth that may change its rotation. Atmospheric and oceanic forces apply torques (axes), which transfer angular momentum between the solid Earth and the atmosphere or oceans. Some of the effects illustrated, such as plate tectonics, are unlikely to contribute significantly to Earth rotation variations at seasonal to subseasonal time scales. [Adapted from (*3*)]

If total angular momentum of the Earth system is conserved, it follows that when the solid Earth loses angular momentum (and the LOD increases), another reservoir of angular momentum must have gained. It is now well known that predominantly the atmosphere is that reservoir. Numerous studies over the past two decades have shown that, to good approximation, the solid Earth and atmosphere simply trade angular momentum with one another over a variety of time scales, ranging from days to years. This is the conclusion to be drawn from figure 2A in the report by Marcus *et al.* (*1*).

There are, of course, additional reservoirs of angular momentum in the Earth system, including the oceans, polar ice sheets, and others, as illustrated in the figure. Not all of these are active on all time scales, and only those involving air and water are likely to be important at seasonal to subseasonal scales. Marcus *et al.* show that, after the atmosphere, the oceans are the next most active reservoir, at seasonal and shorter time scales. The demonstration is accomplished by forming

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the sum of atmospheric angular momentum variations (from a global numerical weather forecast model) and solid Earth changes from LOD data. The sum is small but not zero, and the residual is an estimate of the angular momentum variation within all other reservoirs. The problem is to determine which reservoir (oceans, polar ice, and so on) is most important. To verify that the oceans are dominant, they use ocean general circulation models as a substitute for knowledge of the three-dimensional distribution of currents and mass within the global oceans. They numerically integrate model currents and mass redistribution and subtract the mean values to predict ocean angular momentum changes. The predictions are well correlated with the observed residual and have approximately the correct magnitude, providing convincing evidence that the oceans are the main source.

What developments can be expected to follow from this newly available measure of ocean variability? In the first place, ocean angular momentum may serve as a useful statistic in the development and validation of numerical ocean general circulation models. There are few other measurable global properties of the oceans, and angular momentum has already served in this capacity in the evaluation of atmospheric general circulation models.

Angular momentum variation may also serve as a measure of the "climate" of the oceans, perhaps in the same way that the Southern Oscillation Index is used to measure the climate of the atmosphere. This possibility is suggested by the discovery in the LOD of a distinct signature of the 1997–1998 El Niño event, as reported by Gipson and Ma (*2*). Although the relative contribution of the oceans and atmosphere to this signature is not yet known, further study will eventually allow the two components to be separated, and a measure of El Niño that includes the full volume of the global oceans will become available to supplement sea level and surface temperature observations.

Like the oceans, there are few globally integrated measures of variability in other important elements of the Earth system, such as polar ice and continental water storage. As a better understanding of variability in oceanic angular momentum develops, even these smaller participants in the global budget of angular momentum can be studied.

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PERSPECTIVES: NEUROPHARMACOLOGY

Reward for Persistence in Substance P Research

Claes Wahlestedt

Neuropeptides are short chains of amino acids that are used as transmitters in the nervous system in parallel with the better-known small-molecule transmitters, such as acetylcholine and the biogenic amines. During the latter half of this century, many fascinating discoveries about neuropeptides have been made (see timeline), but the clinical rewards have been few; thus, skepticism remains as to the medical benefits of neuropeptide research. Moreover, some neuroscientists believe that many of the neuropeptides in higher organisms may represent "redundant and clumsy" signaling molecules that have lost their importance, in contrast to the small-molecule neurotransmitter systems that are the targets of many classes of therapeutic agents.

Mammalian neuropeptides act through membrane-bound receptors that are coupled to intracellular signal transduction pathways. Even though a large number of receptors have been cloned and characterized in recent years and are clearly targets for natural and synthetic agonists, it has been difficult to assess the potential therapeutic utility of antagonists. After all, such antagonists need to compete with endogenous neuropeptides, whose actions, even if excessive, may be modulatory and more difficult to demonstrate than those of classical neurotransmitters. A possible exception is the opioid antagonist naltrexone, which is used in the treatment of addiction (*1*).

Substance P, discovered in 1931 by von Euler and Gaddum, is one of the best-known neuropeptides and the most abundant so-called neurokinin (NK) in the mammalian brain and peripheral (notably sensory) neurons. The substance P–preferring receptor, called NK_1, has been pursued as a pharmaceutical target for about 20 years, following from the notion that a NK_1 (or substance P) antagonist might be useful for pain relief. Early advances in this field consisted of peptidic antagonists (*2*) resembling substance P itself, but these molecules suffered from poor bioavailability and were associated with other problems as well. It was only with the appearance of small-molecule NK_1 antagonists in the early 1990s (*3*) that comprehensive clinical testing became conceivable.

Many pharmaceutical companies have developed NK_1 antagonists, some of which penetrate to the brain after oral administration (*4*), and there are even compounds that irreversibly block the actions of substance P. In this busy field, investigators have pursued clinical trials that are based on the proposed efficacy of NK_1 antagonists in a variety of conditions, including pain, inflammation, asthma, emesis, anxiety (see below), and migraine.

The report by Kramer *et al.* on page 1640 of this issue (*5*) shows for the first time that a NK_1 antagonist, MK-869, may be useful in the treatment of moderate to severe major depressive disorder (MDD). In clinical trials carried out at four sites, MK-869 was found to be safe and well tolerated, and its efficacy in MDD, at the single dose studied (300 mg once daily), was comparable to that of the serotonin uptake inhibitor paroxetine (20 mg daily, a moderate clinical dose). Moreover, these phase II data indicate that the side effect profile of MK-869 may differ from that of paroxetine; in particular, the NK_1 antagonist caused a lesser degree of sexual dysfunction.

This study offers hope for depressed patients who experience incomplete efficacy or distressing adverse effects when treated with currently available drugs. Although these individuals may not be so concerned about exactly how their symptoms are being alleviated, the scientific community will be intrigued by the mechanism of action of this new class of potential antidepressant drugs. Kramer *et al.* (*5*) have done as good a job as possible in arguing that NK_1 antagonism indeed underlies the beneficial actions. They document a correlation between animal behavioral data, chiefly NK_1 antagonist–mediated suppression of isolation-induced vocalization responses in guinea pigs [referred to as "antidepressant-like profile" in (*5*)], and the clinical efficacy in patients with MDD.

How then does the NK_1 antagonist affect the brain, and how different is its action from that of monoamine uptake inhibitors? The present study indicates that MK-869 does not augment the function of

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