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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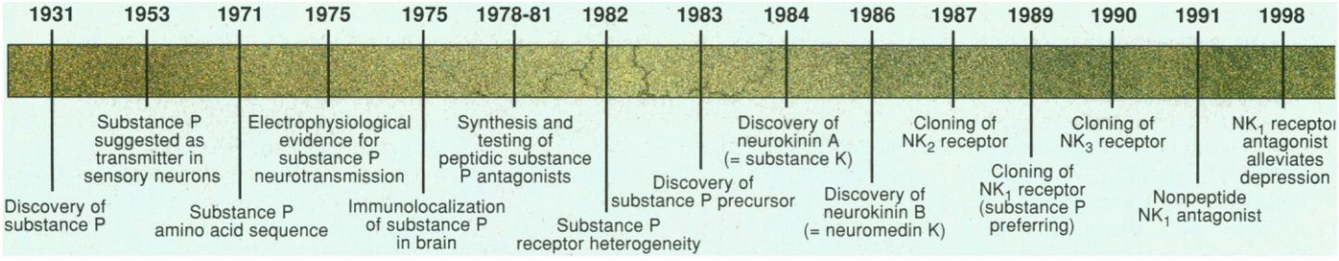

Substance P and related neuropeptides. A few landmarks from discovery to potential therapeutic relevance [(*2*, *3*, *5*, *8*)].

serotonin or norepinephrine (the two neurotransmitter systems that are implicated in the actions of known antidepressants) in animals, nor do these clinically effective antidepressants block NK_1 receptors in vitro. However, additional data on the effective clinical dose will be needed because the 300-mg dose of MK-869 (which likely produces micromolar plasma levels) is arguably high, especially in view of the fact that NK_1 receptor blockade is seen at subnanomolar concentrations in vitro. As a result, there will be some speculation as to whether NK_1 receptor blockade is the only molecular site of MK-869 action in humans with MDD. Moreover, the bulk of the animal data presented in (*5*) relates to acute doses, yet the clinical efficacy of MK-869 was expressed after 2 to 3 weeks, which does not appear to distinguish this compound from known antidepressants and may suggest a "final common pathway" mechanism.

An enticing possibility from the present study (*5*) is that a NK_1 antagonist might also be useful clinically as an anxiolytic agent; this warrants further investigation. On the basis of animal studies, substance P was already known to be present within neuronal circuits (amygdala, hypothalamus) that mediate central stress responses, and it was suggested that a NK_1 antagonist might thus be useful to treat stress and anxiety (*6*, *7*). In fact, another NK_1 antagonist, GCP-49823, was discontinued in a phase I trial aimed toward treatment of anxiety. Interestingly, the clinical data with differential time course of antidepressant and anxiolytic actions of MK-869 [see (*5*)] do not exclude the possibility that the antidepressant effects of the NK_1 antagonist are independent of its anxiolytic effects.

What lessons can be learned for the future discovery and development of pharmaceutical agents? In the field of psychiatric drug discovery, with its shortage of reliable animal models, the argument of a tight link between animal and human data (*5*) will be well received. However, there will be continued debate regarding which findings concerning neurotransmitter actions in animals have a clinical correlate. Only a fraction of the observations made in animals can be extended to costly clinical trials, no matter how spectacular the animal data may be and how pharmacokinetically attractive the compounds at hand. Phenomenological observations during the 1980s (changes in the levels of neuropeptides and their receptors after drug or other treatment in animals; changes in levels of neuropeptides or neuropeptide receptors during human disease) and the 1990s (comparison of a knockout mouse phenotype to human pathophysiology; the influences of genomic polymorphisms on function) are generally an insufficient basis for making rational decisions.

Finally, with respect to NK_1 antagonists, the pharmaceutical industry must be commended for its persistence. However, if this class of compounds indeed finds a role in the pharmacotherapy of depression, then the total expenditures must still be assessed on the basis of the many years of research and failed clinical trials that pursued other (and arguably more intuitive) directions.

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PERSPECTIVES: SIGNAL TRANSDUCTION

Routing MAP Kinase Cascades

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Cells are constantly bombarded by external signals that regulate their growth, differentiation, and stress level. To respond properly to these signals, eukaryotic cells assemble cascades of highly conserved protein kinases (mitogen-activated protein kinases, MAPKs, and their activator kinases), which form the central elements of signal transduction pathways that lead to and activate transcription factors in the nucleus and other effectors throughout the cell (*1*). Cells contain multiple MAPK cascades that can use subsets of the same kinases yet activate different effector proteins, depending on the stimulus. This sharing of kinases makes it critical that the cell properly route the various signals to prevent cross talk between pathways. Yeast cells seem to have solved this problem with the use of scaffolding proteins like Ste5, by forming multienzyme complexes with kinases that are used by more than one pathway and are therefore shared (*2*). On pages 1671and 1668 of this issue, Whitmarsh *et al.* (*3*) and Schaeffer *et al.* (*4*) extend this mechanism to mammalian cells by identifying two proteins, JIP-1 and MP1, that help route two different MAPK cascades. Their findings point to the universal function of scaffolding/adapter proteins in the assembly of information highways inside cells.

The core elements of a MAPK module are three sequentially activated protein kinases, named after the last kinase in the series (see the figure) (*1*). A module can be activated by multiple stimuli and more than one receptor. MAPKs and their activators MAPK kinases are quite homologous within their respective subgroups, while MAP kinase kinases include at least four subtypes—Raf, MEKK, mixed lineage kinases (or MLKs), and Mos. The six MAPKs, seven MAPK kinases, and seven MAPK kinase kinases thus far defined in mammalian cells, set the stage for potential cross-regu-

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