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Richard Wurtman M.D.
Professor of Neuropharmacology Emeritus

Department of Brain and Cognitive Sciences
Building: 46-5023
Lab: Wurtman Lab
Email: dick@mit.edu

Effects of Drugs, Foods and Diseases on Brain Neurotransmitters and Behavior

My goal is to discover safe and effective treatments for brain diseases. I do this by 1) doing fundamental research to identify a previously-unsuspected control mechanism involving brain chemistry; 2) confirming that this mechanism also works in the human brain; 3) identifying a disease in which this mechanism seems not to be operating properly; and 4) doing pilot studies to see whether a possible new treatment, based on these discoveries, actually works. Examples of fundamental principles we have discovered are the facts that 1) certain food constituents affect the chemistry of the brain, and 2) melatonin is a hormone, which is secreted at nighttime, and which promotes sleep. New treatments that have been based on this "translational research" include: 1) melatonin to promote sleep; 2) REDUX (dexfenfluramine) to treat obesity; 3) SARAFEM (fluoxetine) to treat the premenstrual syndrome; 4) Citicoline- which is currently in large-scale, Phase III testing, to treat strokes; and 5) a protein/carbohydrate mixture to enhance the efficacy of L-dopa in treating Parkinson's Disease.

a) Melatonin

It is now recognized that melatonin, the hormone secreted by the pineal gland, has the important role of telling us when to fall asleep, and helping us to remain asleep. This recognition- as well as the knowledge that giving people low doses of melatonin can be used to treat insomnia -have their origins in research done over the past several decades in our laboratories.

Initially in studies on rats, we showed that a) melatonin is a true hormone; b) that it is normally produced at nighttime; and c) this daily rhythm in melatonin synthesis normally is generated by the environmental light cycle: light, acting via the eyes, inhibits melatonin synthesis. Subsequent studies in the MIT Clinical Research Center showed that in humans, like rats, the hormone is produced at nighttime but not during the daytime. Moreover, in humans, nighttime melatonin

production was found to decrease markedly with age, such that in most people over the age of 50, instead of having blood levels rise from 10 to 150 (picograms/ml) at 10 PM - midnight, they rise only to 20 or 30.

We suspected that the nighttime rise in blood melatonin levels might allow this rhythm to serve as a time signal to the brain, and that this signal might be used in turning on and maintaining sleep. Finally, in 1993-1994, we showed that if young people received tiny doses (0.3 mg orally) of the hormone in daytime- when blood melatonin levels are very low - they became sleepy and fell asleep. (The sleep thus produced is normal, electroencephalographically. And the effect of the melatonin in producing sleep is independent of its ability to shift rhythms.) The correct dose of melatonin for this purpose, 0.3 mg, is just sufficient to raise blood melatonin levels to their nocturnal range, but very much lower than the dose sold for various unproved purposes in many health-food stores.

Older people often complain of insomnia, particularly difficulty in staying asleep, and in falling back to sleep after they awaken at night. Doses of melatonin which give them "youthful" blood melatonin levels correct this insomnia.

b) Alzheimer's Disease

A generally-held if unproved view of Alzheimer's Disease is that the brain changes and dementia result from toxic effects of an abnormal protein, called amyloid, which is a polymer of a small fragment (A-beta) of a protein (APP) that is produced normally in all cells. Hence a major goal of researchers hoping to treat this disease is to find drugs that will decrease the formation of A-beta from APP, and increase the production of APP's other major metabolite APPs ("soluble APP"). Using cell cultures, we have shown that the synthesis of APP, and the proportions of this protein that are broken down to A-beta or to soluble APP, are under the control of particular neurotransmitters and the "second messengers" they generate. For example, the neurotransmitters acetylcholine, serotonin, and glutamate act via particular receptors, and the second messenger diacylglycerol, to promote the breakdown of APP to soluble APP, and to suppress its breakdown to A-beta. (Most recently we have shown that activating brain serotonin (2A/2C) receptors in intact animals also promotes the "non-amyloidogenic" breakdown of APP.) In contrast norepinephrine and prostaglandins, acting by some of their receptors and the second messenger cyclic AMP, promote the synthesis of the APP molecule. Using drugs that act on these neurotransmitter receptors, it should be possible to block the formation of APP and all its metabolite, or promote the formation of soluble APP and suppress that of A-beta (and amyloid). We hope that these technologies will become used to diminish the amount of amyloid in the Alzheimer's Disease brain. Conceivably, this may ameliorate the dementia of the disease.

c) Precursor Control of Brain Phospholipid Synthesis

Over the years we have found that the rates at which brain cells produce a number of important compounds, for example the neurotransmitters serotonin, dopamine, and acetylcholine - normally depend on brain concentrations of their precursors (tryptophan, tyrosine, and choline). It now appears that the syntheses of phosphatidylcholine [PC] and the other major membrane phospholipids also depend on precursor availability. The main circulating precursor is cytidine (or, in humans, uridine), a compound that is not present in the final phospholipid product, but which, when phosphorylated to CTP, controls

a key step in phosphatide synthesis (i.e., the combining of phosphocholine and CTP to form endogenous cytidyldiphosphocholine [CDP-choline]). When cultured neurons are stimulated to produce neurites, for example by exposing them to Nerve Growth Factor, another precursor- diacylglycerol-can also become limiting in phosphatide synthesis.

These observations have led to a new strategy for developing drugs to treat strokes and brain injury, i.e., diminish the ultimate size of the damaged area (which usually expands during the initial week after the stroke, because of the release of toxic compounds, like arachidonic acid oxidation products from nearly dying cells), and facilitate the regrowth of damaged axons and synapses by surviving neurons, by promoting the synthesis of PC (which sopps up free arachidonic acid). Both effects can be obtained experimentally, by giving a drug, Citicoline, that breaks down to blood choline and cytidine (uridine in humans), or by giving a constituent of infant formulas, UMP, that raises blood uridine levels. The blood changes increase CTP and phosphocholine levels in the brain, promoting the incorporation of excess free arachidonic acid into PC and thus increasing neuronal membranes.

More recently, we have proposed additional uses for the precursor control of brainphospholipid, which arise from the actual increases in the quantities of membrane phospholipids, per brain cell, that giving the precursors can produce. We find that this treatment causes a specific increase (by up to 40%) in the amount of synaptic membrane (and increase dendritic spine formation.) Hence, it may be useful in treating brain diseases in which the actual number of certain synapses is deficient. This possibility is currently being tested in subjects with early Alzheimer ' s Disease.

This possibility was tested in 2008 in an initial large-scale clinical trial, involving 224 patients with mild Alzheimer's Disease, treated for twelve weeks with a placebo or with the mixture previously shown to increase brain synaptic membrane and dendritic spines in lab animals (i.e., "Souvenaid, which contains uridine monophosphate, docosahexaenoic acid, choline, plus vitamins that promote endogenous hepatic choline synthesis). Patients receiving this mixture satisfied a primary endpoint, exhibiting a statistically-significant improvement in cognitive scores (modified Wechsler test), and no side-effects. A second, larger clinical trial, involving patients with mild to moderate Alzheimer's Disease, and also receiving a drug (a cholinesterase inhibitor or memantine) was initiated in April, 2009 at 40 sites in the United States; it is anticipated that this study will be completed early in 2010.

Scheltens P, Kamphuis PJ, Verhey FR, Olde Rikkert MG, Wurtman RJ, Wilkinson D, Twisk JW, Kurz A. Efficacy of a medical food in mild Alzheimer's disease: A randomized, controlled trial. Alzheimers Dement. 2010 Jan;6(1):1-10.e1.

Mischoulon D, Pedrelli P, Wurtman J, Vangel M, Wurtman R. Report of two double-blind randomized placebo-controlled pilot studies of a carbohydrate-rich nutrient mixture for treatment of seasonal affective disorder (SAD). CNS Neurosci Ther. 2010 Spring;16(1):13-24. Epub 2009 Sep 21.

Wurtman RJ, Cansev M, Sakamoto T, Ulus IH. Use of phosphatide precursors to

promote synaptogenesis. Annu Rev Nutr. 2009;29:59-87. Review.

Cansev M, Marzloff G, Sakamoto T, Ulus IH, Wurtman RJ. Giving uridine and/or docosahexaenoic acid orally to rat dams during gestation and nursing increases synaptic elements in brains of weanling pups. Dev Neurosci. 2009;31(3):181-92. Epub 2009 Jan 15

Additional Publications

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
77 Massachusetts Ave Cambridge, MA 02139
(tel) 617.258.9344