A PHOTOGRAPHIC MEMORY?

THANKS FOR THE MEMORIES

TOKYO—While not everyone needs or wants a photographic memory, the ability to prevent or correct amnesia resulting from injury or disease would be most welcome. To this end, a number of Japanese pharmaceutical firms are developing some promising neurologically active agents that affect learning and memory.

One such company is Takeda Chemical Industries (Osaka). At Takeda's Biology Research Laboratories in its Research and Development Division, researchers have been studying thyrotropin-releasing hormone (TRH) for a number of years. TRH, a tripeptide previously labeled a thyroid-regulating pituitary hormone, has been shown to be distributed throughout the brain, and to have a number of central-nervous-system actions independent of its endocrine function. In particular, TRH causes marked electrophysiological and behavioral excitation in animals made centrally depressive by injecting such drugs as pentobarbital, ethanol, and reserpine, as well as by inducing brain lesions. TRH exerts its effects by stimulating the release of the neurotransmit-

ters acetylcholine, dopamine, norepinephrine, and serotonin. TRH has also been shown to have neurotrophic action.

Effective against Alzheimer's?

Alzheimer's Disease is characterized by a progressive malfunction of the neurons of the brain, which results in memory disorders and other psychological symptoms associated with the deterioration of neurotransmission. Consequently, TRH may be useful for treatment of dementia, including that brought about by Alzheimer's. In clinical trials of TRH, however, the therapeutic effect has been restricted: TRH has a short plasma half-life, which results in short-lived pharmacological action. Takeda researchers have addressed this by developing a proprietary sustained-release TRH formulation (TRH-SR) that provides continuous TRH delivery over a two-week period. TRH-SR has shown memory-ameliorating effects in various animal models at low dosages.

Most recently, in a paper submitted to *Psychopharmacology*, Masao Miyamoto

and his coworkers described the effects of TRH-SR on learning impairments induced in mice and rats by scopolamine, cycloheximide, and ethylcholine aziridium ion (AF64A), a cholinergic neurotoxin.

Scopolamine and cycloheximide were used to significantly impair the test animals' passive avoidance response. In this case, their learned avoidance of electrical shock. TRH-SR (0.04 and 0.2 mg/kg/day) given subcutaneously seven or eight days before the acquisition trial, or learning training, was shown to markedly ameliorate drug-induced amnesia in mice. However, repeated TRH administration over the same period had no significant amnesia-ameliorating effects. The paper further reported that lateral-ventricle injection of AF64A into rats resulted in apparent deficits when the animals later performed passive-avoidance tasks, and that immediate postinjection delivery of TRH-SR ameliorated this impairment. Moreover, AF64A-treated rats showing significant impairment in a water-maze learning task initiated two weeks after injection exhibited significant performance improvement when given postinjection TRH-SR.

Effective against aging?

Miyamoto and his coworkers have also found (as reported in a paper to be published in *Physiological Behavior*) that low doses of TRH-SR reverse learning impairment in senescence-accelerated mice. These doses also reduce anxiety-like behavior such as depressed motor function. Moreover, they have found that low-dosage TRH-SR treatment has a significant ameliorating effect on learning impairments in aged rats (manuscript in preparation). They have found, however, that while a single high-dosage (5-20 mg/kg) TRH injection produces cognitive-enhancing effects, intermittent administration of low dosages has no significant effects, and continuous infusion leads to the greatest improvement, even better than single-injection delivery. Since it has been suggested that cognitive-function deterioration in Alzheimer's and senile dementia of the Alzheimer's type may be closely related to cholinergic dysfunction, Miyamoto *et al* conclude, "TRH-SR, which continuously activates the cholinergic system, may be useful for age-related memory impairment, including Alzheimer's disease and senile dementia of the Alzheimer's type." Takeda hopes to market TRH-SR by 1997.

—Stuart M. Dambrot

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