Neuroscience Today, Neurology Tomorrow

Neurology is the center of what might more properly be labeled "the clinical neurosciences," a term that emphasizes the importance of technological innovation and scientific discovery, and recognizes that the application of neuroscientific discoveries occurs not only in neurology, but in neurosurgery, neuroradiology, and other fields as well. Neurologists at the bedside and at the bench are at the forefront of innovation and discovery, translating neuroscience into clinical practice. Our patients require this. In our new column, "Neuroscience Today, Neurology Tomorrow" we highlight discoveries that promise to advance the clinical frontier. We invite you to send your reactions/responses to this column to www.clinicalneurologynews@elsevier.com.

—Richard J. Caselli, M.D.

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Granulocyte-Colony–Stimulating Factor in Repair of Ischemic Stroke

Granulocyte-colony–stimulating factor and epidermal growth factor plus erythropoietin show promise for treating ischemic stroke, according to two separate studies presented at the annual meeting of the Society for Neuroscience.

In experiments with rats that underwent a transient occlusion of the middle cerebral artery, the volume of infarct significantly decreased when granulocyte-colony–stimulating factor (G-CSF) was administered either 2 or 4 hours after the onset of ischemia, reported Rico Laage, Ph.D., of Axaron Bioscience AG, Heidelburg, Germany. Similar results occurred when G-CSF was administered 1 hour after the onset of ischemia caused by transient occlusion of the common carotid artery and distal middle cerebral artery. G-CSF is normally used to treat neutropenic conditions.

In vitro studies have shown that G-CSF reduces apoptotic activity in human neurons and that the G-CSF receptor is expressed in the human brain and is upregulated in infarcted areas shortly after stroke in humans.

In Germany, Axaron is conducting a multicenter, randomized, double-blind, placebo-controlled phase II trial of G-CSF in patients who suffered an acute ischemic stroke in the region of the middle cerebral artery within the last 12 hours and are not receiving tissue plasminogen activator. Following a 3-day intravenous infusion of G-CSF, investigators measure thromboembolic complications up to discharge or day 4 and infection or other serious adverse events after 4 weeks. Neurological outcome is measured at 4 and 12 weeks after treatment while the growth of the ischemic lesion is measured from baseline to 3 months after treatment with MRI.

In another study, Trudi Stickland, at the University of Calgary, and her associates found that epidermal growth factor (EGF) and erythropoietin (EPO) stimulated the proliferation and differentiation of endogenous neural stem cells and repaired infarcted stroke regions in rats. The researchers induced ischemic strokes in the primary motor cortex that affected the forepaw contralateral to the side of the brain that was lesioned.

Intracerebroventricular infusions of EGF and EPO significantly increased gross motor functioning of the affected forepaw when rats spontaneously explored a cylindrical cage and fine motor functioning in a trained task that involved reaching through a narrow slot to grasp a food pellet.

Rats who received only serum albumin recovered very little function. After these behavioral tests (50 days after the stroke), the researchers found that stem cells had migrated to the lesion site in the motor cortex of rats that received EGF and EPO and initiated regrowth of cortical tissue. "We're not sure that these new neurons in the lesion site are necessarily functional," Ms. Stickland said. Future experiments will determine if the new tissue is establishing new neural connections or is secreting agents that help the surrounding tissue take on new functions.

Dr. Caselli's comment: Neurologists have floundered for decades with anticoagulant therapies and have emphasized primary prevention in populations that already have advanced risk. The advent of IV recombinant tissue plasminogen activator (rTPA) ushered in the era of immediate, definitive intervention. For the first time, minutes mattered. The notion of "brain attack," if not exactly born, finally let out a long-awaited cry that the world heard. Neurology has a long-standing reputation of being more of a diagnostic than a therapeutic specialty, leading many doctors and patients to have a nihilistic view of neurologic therapeutics. Invasive cerebrovascular techniques such as intraarterial TPA, stent coils, and other devices are changing that perception. In the two studies described above, different forms of growth factors and apoptosis inhibitors reduced stroke size when given immediately in rats.

While an intracerebroventricular avenue will not suffice clinically, especially for patients who may be eligible for thrombolysis, the notion of treating a patient with substances that immediately inhibit cell death and promote regeneration is a logical and potentially powerful next step. While more work is clearly needed, it is encouraging that some substances, such as G-CSF have reached the stage of human trials.

Parkinson's Immunotherapy Targets α-Synuclein Aggregates

Immunotherapy that targets aggregates of α-synuclein protein in dopamine neurons points toward a potential pathway for treating Parkinson's disease, Dr. Eliezer Masliah reported at the annual meeting of the Society for Neuroscience.

Aggregates of oligomeric protofibrils of α-synuclein, which is highly concentrated in presynaptic boutons and plays an important role in neurotransmitter release, may contribute to the synaptic damage and degeneration found in disorders with Lewy bodies, such as Parkinson's disease. "There is a clear relationship between the distribution and aggregation of α-synuclein in cortical and subcortical regions and the patterns of clinical manifestations," said Dr. Masliah of the University of California, San Diego.

He and his associates used human recombinant α-synuclein to vaccinate transgenic mice that express human α-synuclein and show the characteristic accumulation of abnormal α-synuclein oligomers in plasma and synaptic membranes and motor deficits of Lewy body disease and Parkinson's disease. The animals developed relatively high titers of antibodies to α-synuclein, which showed high affinity to α-synuclein aggregates in immunoblot assays and tissue sections. The mice that produced high-affinity antibodies accumulated fewer α-synuclein aggregates, which was associated with reduced neurodegeneration. The α-synuclein aggregates appear to be degraded via lysosomal pathways. The results suggest that α-synuclein antibodies might directly interact with oligomers of α-synuclein at the synaptic membrane or they might bind to receptors, resulting in the endocytosis of the antibodies with the α-synuclein complex, Dr. Masliah said.

No effects were seen on endogenous murine α-synuclein or on other α-synuclein–related markers that are present in the synapse, such as β-synuclein. No severe inflammatory effects were observed in the mice during the experiments, but because of the risk of using active immunization in humans, Dr. Masliah and his colleagues have been developing a passive immunization protocol for future experiments.

Dr. Caselli's comment: The strategy employed by Masliah and colleagues is reminiscent of the amyloid vaccination strategy also initially tested in a transgenic mouse model, and then extended into human trials. Masliah et al. are wisely taking the next step based on the Alzheimer's vaccination experience in which 5% of vaccine recipients developed an autoimmune meningoencephalitis and cerebral vasculitis that resulted in clinical deterioration and prompted premature termination of the trial. A passive vaccination strategy is now underway for Alzheimer's disease, and given the groundbreaking work of Masliah and colleagues, we may anticipate a similar trial for Parkinson's disease in the future. This is a powerful new approach, but clinical efficacy and safety still await further experience.

Protein-Stimulated Neural Stem Cell Repair in Parkinson's Model

The protein compound sNN0031 restored nearly all function and normalized dopamine transporter levels in a rat model of Parkinson's disease for at least 10 weeks by activating endogenous stem cell repair in the striatum, Olof Zachrisson, Ph.D., reported at the annual meeting of the Society for Neuroscience.

To mimic the effects of Parkinson's disease, Dr. Zachrisson of NeuroNova, Stockholm, and his associates injected 6-hydroxy dopamine unilaterally into the right median forebrain bundle of rats, which reduced dopamine transporter binding by 75% in the striatum. When the lesioned rats were given amphetamine, they rotated toward their lesioned side, a sign of an imbalanced dopamine system.

Five weeks later, lesioned rats and those that were given a sham injection received an intracerebroventricular infusion of sNN0031 or a vehicle for 2 weeks. Afterward, lesioned rats on sNN0031 showed significantly more improvement in rotational behavior than rats given vehicle; improvement continued up to 10 weeks after the drug had been administered. Lesioned rats on sNN0031 had a significantly improved level of striatal dopamine transporter binding 10 weeks after treatment, Dr. Zachrisson said.

sNN0031 induced endogenous stem cell proliferation in the ventricular wall adjacent to the medial striatum and neurogenesis in the striatum; the investigators have not yet determined if the new neurons are producing dopamine. At a press conference, one of the investigators, Dr. Anders Haegerstrand, also of NeuroNova, said that sNN0031 is already approved by the Food and Drug Administration for a non-CNS indication, albeit in a different form and dose. He would not say what disease the drug is normally used to treat or what its composition is for proprietary reasons.

Dr. Caselli's comment: That an existing compound has demonstrated neuroregenerative potential in this rat model is encouraging and warrants further exploration, although there is also some reason for caution. First, the lesioned rats in this study are not a model for progressive degenerative parkinsonism, but rather for a static basal ganglia lesion. Second, intracerebroventricular delivery of the agent is not an ideal access point for clinical therapy, especially after the failed adrenocortical transplantation trials. Third, much more work needs to be done to elucidate how the behavioral changes in the rats came about. Fourth, the long-term effects of enhancing CNS stem cell activity (or potentially encouraging other cellular populations as well) need to be determined. For example, is there a long-term risk of brain tumors? Fifth, given that this compound is FDA approved, much more information must be available about its clinical properties, side effects, and appropriateness for the intended patient population. These and other caveats aside, the results of this study are exciting for patients and researchers alike. ■

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