TABLE 444e-3 NEUROTROPHIC FACTORS

Neurotrophin family	Transforming growth factor β family
Nerve growth factor	Glial-derived neurotrophic family
Brain-derived neurotrophic factor	Neurturin
Neurotrophin-3	Persephin
Neurotrophin-4	Fibroblast growth factor family
Neurotrophin-6	Hepatocyte growth factor
Cytokine family	Insulin-like growth factor (IGF) family
Ciliary neurotrophic factor	IGF-1
Leukemia inhibitory factor	IGF-2
Interleukin 6	
Cardiotrophin-1	

with the severity of autism. A murine model of autism was recently induced in offspring after injecting the pregnant mother with the viral RNA mimic polyinosinic:polycytidylic acid (poly I:C). Remarkably, oral treatment of offspring with *B. fragilis* corrected a range of autistic behaviors in these mice and also improved gut permeability.

NEUROTROPHIC FACTORS

Neurotrophic factors (Table 444e-3) are secreted proteins that modulate neuronal growth, differentiation, repair, and survival; some have additional functions, including roles in neurotransmission and in the synaptic reorganization involved in learning and memory. The neurotrophin (NT) family contains nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), NT3, and NT4/5. The neurotrophins act at TrK and p75 receptors to promote survival of neurons. BDNF is linked to synaptogenesis. Certain polymorphisms are linked to increased risk for Alzheimer's disease (AD), and BDNF is depleted in Huntington's disease. Because of their survival-promoting and antiapoptotic effects, neurotrophic factors are in theory outstanding candidates for therapy of disorders characterized by premature death of neurons such as occurs in ALS and other degenerative motor neuron disorders. Knockout mice lacking receptors for ciliary neurotrophic factor (CNTF) or BDNF show loss of motor neurons, and experimental motor neuron death can be rescued by treatment with various neurotrophic factors including CNTF, BDNF, and vascular endothelial growth factor (VEGF). However, in phase 3 clinical trials, growth factors were ineffective in human ALS. The growth factor glial-derived neurotrophic factor (GDNF) is important for survival of dopaminergic neurons. Direct infusions of GDNF showed initial promise in Parkinson's disease, but the benefits were not replicated in a larger clinical trial.

STEM CELLS AND TRANSPLANTATION

The nervous system is traditionally considered to be a nonmitotic organ, in particular with respect to neurons. These concepts have been challenged by the finding that neural progenitor or stem cells exist in the adult CNS that are capable of differentiation, migration over long distances, and extensive axonal arborization and synapse formation with appropriate targets. These capabilities also indicate that the repertoire of factors required for growth, survival, differentiation, and migration of these cells exists in the mature nervous system. In rodents, neural stem cells, defined as progenitor cells capable of differentiating into mature cells of neural or glial lineage, have been experimentally propagated from fetal CNS and neuroectodermal tissues and also from adult germinal matrix and ependyma regions. Human fetal CNS tissue is also capable of differentiation into cells with neuronal, astrocyte, and oligodendrocyte morphology when cultured in the presence of growth factors.

Once the repertoire of signals required for cell type specification is better understood, differentiation into specific neural or glial subpopulations can be directed in vitro; such cells could also be engineered to express therapeutic molecules. Another promising approach is to use growth factors, such as BDNF, to stimulate endogenous stem cells to proliferate and migrate to areas of neuronal damage.

A major advance has been the development of induced pluripotent stem cells. Using this technique, adult somatic cells such as skin fibroblasts are treated with four pluripotency factors (SOX2, KLF4, cMYC, and Oct4), and this generates induced pluripotent stem cells (iPSCs). These adult-derived stem cells sidestep the ethical issues of using stem cells derived from human embryos. The development of these cells has tremendous promise for both studying disease mechanisms and testing therapeutics. As yet there is no consensus on the best way to generate and differentiate the iPSCs; however, techniques to avoid using viral vectors and use of Cre-lox systems to remove reprogramming factors result in a better match of gene expression profiles with those of embryonic stem cells. Over the years, the field of directed differentiation has used three main strategies to specify neural lineages from human pluripotent stem cells. These strategies are embryoid body formation, coculture on neural-inducing feeders, and direct neural induction. Thus far, iPSCs have been made from patients with all of the major human neurodegenerative diseases, and studies using them are under way.

Although stem cells hold tremendous promise for the treatment of debilitating neurologic diseases, such as Parkinson's disease and spinal cord injury, it should be emphasized that medical application is in its infancy. Major obstacles are the generation of position- and neurotransmitter-defined subtypes of neurons and their isolation as pure populations of the desired cells. This is crucial to avoid persistence of undifferentiated embryonic stem (ES) cells, which can generate tumors. The establishment of appropriate neural connections and afferent control is also critical. For instance, human ES motor neurons will need to be introduced at multiple segments in the neuraxis, and then their axons will need to regenerate from the spinal cord to distal musculature.

Experimental transplantation of human fetal dopaminergic neurons in patients with Parkinson's disease has shown that these transplanted cells can survive within the host striatum; however, some patients developed disabling dyskinesias, and this approach is no longer in clinical development. The possibility that iPSCs will be used in Parkinson's disease was strengthened by studies showing that they can be differentiated into dopaminergic neurons. The dopaminergic neurons were then shown to rescue the parkinsonian phenotype in a MPTP-induced primate model with excellent dopaminergic neuron survival function and lack of neural overgrowth. The correction of tau mutations in iPSC-derived neurons has been shown to reverse the toxic phenotype in dendrite retraction and cell death.

Another new use for iPSCs is to screen drugs as potential treatments for neurodegenerative and other diseases. The feasibility of this has been shown using iPSC-induced macrophages from patients with Gaucher's disease, and verifying the efficacy of protein chaperones in these cells as a means of stabilizing the mutant glucocerebrosidase and increasing its activity and the duration of its effects. Other approaches are to attempt to reduce expression of proteins, such as amyloid, tau, and α-synuclein, implicated in the pathogenesis of neurodegenerative diseases. One difficulty has been that reprogramming cells to iPSCs resets their identity back to an embryonic age, which is a hurdle in modeling of late-onset diseases. One approach to this has been to express a fragment of the mutated gene, such as a portion of lamin A, which causes premature aging in progeria. This approach showed that dendrite degeneration and progressive loss of tyrosine hydroxylase expression, as well as enlarged mitochondria and Lewy body precursor inclusions, were induced in iPSC-derived dopaminergic neurons with progerin-induced aging.

Studies of transplantation for patients with Huntington's disease have also reported encouraging, although very preliminary, results. OPCs transplanted into mice with a dysmyelinating disorder effectively migrated in the new environment, interacted with axons, and mediated myelination; such experiments raise hope that similar transplantation strategies may be feasible in human disorders of myelin such as MS. The promise of stem cells for treatment of both neurodegenerative diseases and neural injury is great, but development has