New Innovations: Therapeutic Opportunities for Intellectual Disabilities

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Intellectual disability is common and is associated with significant morbidity. Until the latter half of the 20th century, there were no efficacious treatments. Following initial breakthroughs associated with newborn screening and metabolic corrections, little progress was made until recently. With improved understanding of genetic and cellular mechanisms, novel treatment options are beginning to appear for a number of specific conditions. Fragile X and tuberous sclerosis offer paradigms for the development of targeted therapeutics, but advances in understanding of other disorders such as Down syndrome and Rett syndrome, for example, are also resulting in promising treatment directions. In addition, better understanding of the underlying neurobiology is leading to novel developments in enzyme replacement for storage disorders and adjunctive therapies for metabolic disorders, as well as potentially more generalizable approaches that target dysfunctional cell regulation via RNA and chromatin. Physiologic therapies, including deep brain stimulation and transcranial magnetic stimulation, offer yet another direction to enhance cognitive functioning. Current options and evolving opportunities for the intellectually disabled are reviewed and exemplified.

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Treatment of intellectual disability (ID) is not a new phenomenon. The earliest references to ID date to the Papyrus of Thebes, circa 1500 BC, which includes the first identified records reporting disabilities of the mind.[1] Societal viewpoints, which have varied widely over time and between groups,[2,3] largely determine the general response to people with ID, as well as the degree to which society invests in assisting affected individuals. From a financial perspective, ID is a major problem; in the United States in 2006, 11% of total government spending was for disability support, and this is expected to increase.[4] With the realities of deinstitutionalization, society has had to accept a greater awareness of the issue, as individuals previously kept "away" are now integrated into families and the community. Thus, there are both financial and social imperatives to improve services for this group and provide stimulation for research into treatment.

Modern Understanding of Biology

ID is not a single entity, but reflects a myriad of different disorders. Genetic causes alone may number in the thousands.[5] This complicates our understanding, as we are not dealing with a discrete pathology but rather a collective with similar phenotypes. Furthermore, the terms used are themselves not truly descriptive. ID, the currently accepted American term (replacing mental retardation), is socially rather than scientifically derived, and limited in its precision. The new International Classification of Diseases (11th revision) categorization recommends "intellectual developmental disorder."[6] Our understanding of how learned memories are stored in the brain is still fragmentary,[7–9] but learning processes appear to converge upon the ability to appropriately develop and modulate synaptic junctions in the brain.

Proper synaptic function, and hence normal intellectual function, depends upon two major components: (1) development of the nervous system and (2) functioning of the neurons and their network. Cognition appears to be particularly dependent upon both normal synaptic connections and the ability to modulate these connections in response to new stimuli, adapting as necessary. If the underlying anatomy of the brain is abnormal, for example, in a gross brain malformation like

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holoprosencephaly, the abnormal anatomy precludes the correct neural circuitry. Malformations affecting later developmental stages, such as neuronal migration disorders, similarly result in ID by disrupting normal patterns of synaptic connectivity.[10] However, the majority of genetic causes of ID appear to disrupt the essence of the neuron's function, namely, its ability to send effective signals to other neurons. This effect is the strengthening (long-term potentiation) or weakening (long-term depression) of specific synaptic connections and their ability to be further altered in response to future stimuli.[11] This appears to be the basis upon which memory and response to learning can occur, as stimuli and responses are trained into specific routes. Defects in this ability to control synaptogenesis underlies many intellectual disabilities.[12–14]

The failure of appropriate signaling between neurons across the synaptic junctions of dendritic branches is the central deficit in many cases of ID, as increasing data show. Perhaps the best example is fragile X. The FMRP protein product of the fragile X gene, *FMR1*, is critical to dendritic, and hence synaptic, maintenance and plasticity. FMRP transports critical RNA transcripts from the nucleus to dendrites.[15] It also regulates translation of these transcripts by inhibition of the mGluR5 glutamate receptor.[16] This receptor stimulates sp6 kinase translation for production of the proteins which create the dendritic outgrowths that interface with other neurons and allow signals to cross at the dendritic synaptic junction. Normally, this process is carefully regulated. In fragile X, the loss of FMRP results in unfettered mGluR5 activity and elevated protein translation.[17–19] Abnormal protein translation is associated with abnormal dendritic morphology and abnormal patterns of synaptic plasticity, with profound effects on the capacity of affected individuals to learn and respond appropriately. An increasing number of genes linked to ID, involving a range of synaptic mechanisms, are being identified, whether they affect synaptogenesis directly[20–26] or regulate anatomical patterns or consequent functioning.[27,28] These pathways offer targeted treatment opportunities that focus on the molecular underpinnings of ID.

Currently Available Therapies

Much of current treatment is focused on environmental optimization. This includes individualized education plans, as well as minimizing complicating comorbidities (visual, sleep, pain, etc). This approach has provided significant improvements, as exemplified by the improved prognosis for Down syndrome.[29,30] Although central to current management, it is not curative.

Specific treatments for improving ID at a biological level do exist, and have been around for some time. For example, dietary restriction for newborns identified with phenylketonuria (PKU) [who if left untreated develop an intelligence quotient of <30] were first attempted by Bickel >50 years ago.[31] Successful treatment of PKU has become a paradigm for newborn screening and has produced a generation of healthy adults with PKU. Preventative treatment can take place even earlier; examples of prenatal treatments include education around avoidance of neurotoxic compounds such as alcohol or treatment of maternal hypothyroidism.[32] Preventative therapies have changed the way we manage pregnancy and newborns, and within the inborn errors of metabolism community, instituting guided management at diagnosis has improved outcomes for a range of disorders.[33–35] For some disorders, such as Hurler syndrome, newborn screening offers early diagnosis with the opportunity for meaningful treatment for cognition.[36] The potential benefit is less clear for disorders for which cognitive treatments are not yet available, such as Rett syndrome[37] or fragile X, although other aspects of such disorders may benefit.[38]

Enzyme replacement therapy (ERT) has improved care for some metabolic disorders. As alluded to above, when coupled with stem cell therapy as a treatment for Hurler syndrome (mucopolysaccharidosis type 1), very young children have shown improved cognition.[39] Interestingly, for previously lethal conditions such as Pompe disease, in which ERT has changed prognosis, there appears to be unexpected intellectual sparing. As glycogen stores accumulate in the brain and the ERT does not cross the blood–brain barrier, it was anticipated cognition would suffer, as seen in other storage disorders. However, this possibility fortunately appears not to have been realized, at least to midchildhood.[40,41] Unfortunately, ERT and metabolic amelioration are often insufficient in other disorders. Cognitive deficits remain for many metabolic disorders despite treatments. Treatment may exert a partial effect, as for some with organic acidemias,[42] but seems less efficacious in other conditions, such as tyrosinemia or the urea cycle defects.[43,44] Some treatments aim to improve on existing therapies, such as sapropterin dihydrochloride (BH4) in PKU. Although dietary treatment is effective, it is challenging to maintain, and compliance falls off over time, which has consequent effects on higher cognitive functions. BH4, a cofactor for phenylalanine hydroxylase (the defective enzyme in most cases of PKU), has been shown to benefit some patients.[45–47]

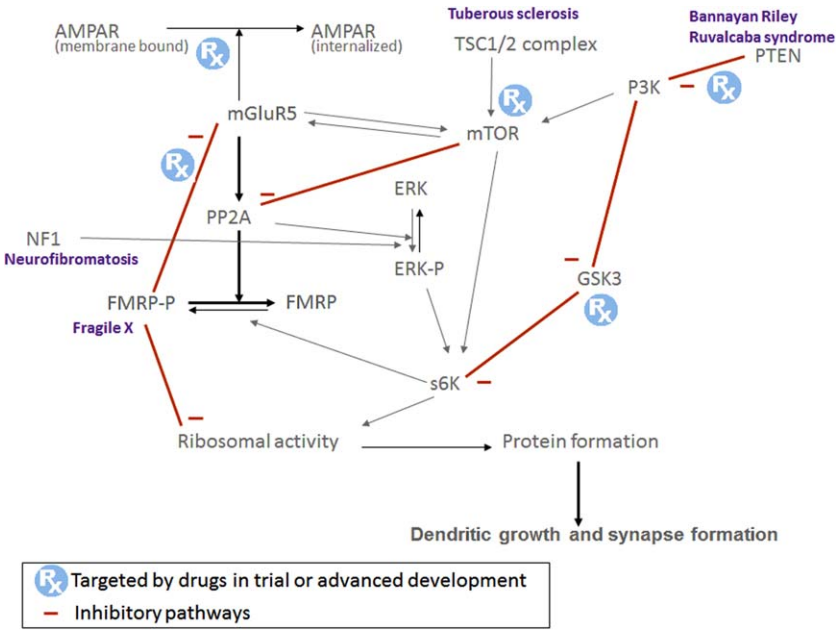

FIGURE 1: Relative positions of disorders in the upstream pathways and target regions of potential therapeutic agents currently undergoing clinical trials or under active research with a view toward clinical trials. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

Therapeutic Pipeline in 2013

Whereas the majority of clinical trials still focus on supportive management, such as treatment of epilepsy, pain, and comorbidities (see ClinicalTrials.gov for details), an increasing number of trials focus on treatment of the underlying defect, via re-equilibration of the biochemical imbalance that results from genetic mutations. This method of targeted treatments is currently in trial for a number of disorders, and may offer opportunities to directly improve cognition. The majority currently in trial share pathways involved in control of dendritic growth and synaptogenesis.

A critical question for these and other treatment options is when to intervene. For some disorders, where damage occurs early, such as PKU, the earlier the treatment the better; but for others, such as Rett syndrome or fragile X, this may not necessarily be the case.

Concern about potential iatrogenic damage to the developing brain of neuroactive treatments needs to be weighed against excessive delay, when reversibility of the damage may be limited. Timing for these treatments will likely be disease specific. However, as research trials work their way down the age spectrum, the optimal age for treatment initiation and duration of therapy will likely become clearer.

Fragile X

Fragile X is the most common inherited cause of ID, affecting 1 in 4,000 individuals. As discussed above, FMRP regulates dendritic growth, with the γ-aminobutyric acidergic (GABAergic) system being especially sensitive. Lack of FMRP results in unimpeded mGluR5 activity, which causes aberrant dendritic development with mis-signaling, culminating clinically in ID, autism, and psychopathology.[48] This model offers several potential targets. First, GABAergic activity can be increased. The first trial indicating a favorable response using this targeted approach has been carried out using arbaclofen, a $GABA_B$ agonist. Initial results in humans suggest improvement in social function and behavior in individuals with fragile X.[49] In addition, mGluR5-specific antagonist trials have begun (involving AFQ056, RO4917523, and STX107), with a view toward replacing the inhibitory effect of the missing FMRP activity. Although definitive data are not yet available, a phase I trial of the mGluR5 inhibitor fenobam has suggested promising efficacy based on a single dose.[50] Additionally, the antibiotic minocycline, a metalloproteinase inhibitor that seems to have an inhibitory effect on the mGluR5 receptor, appeared in a double-blind study to have some efficacy.[51,52]

Mammalian Target of Rapamycin Pathway

Next to Fragile X, tuberous sclerosis (TS) has probably generated the most activity in the research world of translational neuroscience. TS is a multisystem disorder with significant central nervous system effects, including cognitive deficits. TS is caused by mutations in either *TSC1* or *TSC2*, which encode proteins that form a complex inhibiting activation of mammalian target of

rapamycin (mTOR).[53,54] The protein mTOR, which regulates both mGluR5 and ERK—itself a regulator of pS6kinase translation and central to RNA translation—was identified as a potential target for treatment by a number of groups.[55,56] Several drugs targeting the mTOR pathway are in clinical trial or design, and show promise in both preclinical and clinical trials. These include rapamycin itself as well as related compounds.[57] At this time, everolimus, an inhibitor of mTOR, is currently in trial to assess its role in improving the neurocognitive function of individuals with TS. It is notable that the mTOR pathway interleaves with the fragile X pathway (as shown in Figure 1). Subsequently, a number of other relatively common disorders involving other steps that interact with this pathway have been identified.[58–60] These disorders generally feature ID and autistic symptomatology.[6,61,62] This genetic interconnectedness raises some hope that treatments to regulate the mTOR pathway may help at least some other ID/autistic disorders in which the pathway appears to be indirectly perturbed.[48]

Rett Syndrome/MeCP2

Rett syndrome, a disorder that occurs mainly in girls, is characterized by regression, ID, and distinctive hand movements, and is caused by mutations in the *MeCP2* gene.[63] Milder mutations in *MeCP2* cause a variety of other ID syndromes in both males and females.[64] *MeCP2* encodes a protein that binds methylated DNA. As a regulator of transcription, it appears to have multiple roles, including regulating neural homeostasis genes.[65] In addition, it has a role in synaptogenesis, although by as yet unclear mechanisms.[66] Mouse models for Rett syndrome show abnormal paw movements remarkably analogous to the human defects, and in these mice replacement of MeCP2 restored at least partial function.[67,68] These mouse studies suggested that *MeCP2* does not have essential functions in brain development and that interventions put in place after development was complete could still have potential efficacy. Overexpression of the trophic factor BDNF in a Rett model mouse also appeared to ameliorate the deficit.[69] Insulinlike growth factor 1 (IGF-1) is a proxy growth factor with significant molecular and functional overlap with BDNF and the ability to cross the blood–brain barrier. It has a potential role in Rett syndrome, as it increased survival and function in the mouse model.[70] Following successful phase I studies,[70] a phase II study is underway with cognitive outcome as a secondary outcome measure. Deriving in part from this, NNZ-2566, a synthetic analogue of the N-terminus tripeptide, glycine-proline-glutamate of IGF-1 which has similar effects but better pharmacokinetic properties, is currently in phase I of a clinical trial.[71–73]

Trisomy 21/Down Syndrome

Trisomy 21 is the most common genetic cause of ID. Despite the duplication of an entire chromosome, it is likely that only a small number of genes and other genetic elements are involved in the phenotype of Down syndrome. Immunohistopathology and mouse model studies have identified candidate genes of interest, as well as pathologies that may be amenable to interventions. Vitamin E has been suggested, in some studies, to have utility in Alzheimer disease,[74,75] and is currently in trial to see if it will slow the cognitive decline of older adults with Down syndrome who develop a precocious and severe form of AD in almost all cases. A study using memantine, a glutamine antagonist, suggested limited cognitive improvement in verbal memory in adults with Down syndrome; however, confirmation is required.[76] Perhaps the most interesting direction is the use of agents such as epigallocatechin gallate, which is a polyphenol that modulates *DYRK1A* gene function. *DYRK1A* is located on chromosome 21 and is overexpressed in Down syndrome, and was previously shown to be associated with neurofibrillary tangles and splicing regulation.[77,78]

Unmet Needs

Three primary areas remain particularly challenging for development of treatments. These are: (1) major congenital structural brain lesions (eg, holoprosencephaly, hydrocephalus, and other lesions impacting gross anatomy), (2) ID of unknown etiology, and (3) untreated consequences of known disorders, such as neurodegenerative conditions and other causes of neural damage (eg, inborn errors of metabolism such as methylmalonic acidemia and others, kernicterus, etc).

Hopefully, as understanding of ID continues to improve and opportunities for specific disorders are developed, the ramifications of these developments will extend to these as yet unaided areas. For this, it may also be that new perspectives must emerge before we can begin to tackle the problem therapeutically.

Possible New Directions for Research

Conventional Drugs, New Uses

As awareness of the underlying neurobiochemical pathway deficits improves, possible uses for already-approved medications are increasingly being realized. For example, application of targeted drugs such as lithium and baclofen have shown some improved cognitive performance in a Down syndrome mouse model.[79–81]

MicroRNA

MicroRNAs are a class of noncoding RNAs that bind to mRNA and regulate their translation. Over half of microRNAs are neurally expressed.[82] Many appear to

have broad regulatory roles in cognitive processes, including regulation of neuroplasticity[83] and protein levels (eg, BDNF and the N-methyl-D-aspartate receptor NR2A in ID disorders[84]). They may function as intermediate molecules in regulatory functioning of critical genes such as *MeCP2* in Rett syndrome[85] or for FMRP in controlling dendritic spine morphology in animal models of fragile X.[86] Therapeutic microRNAs, acting at the ribosome, may inhibit indiscriminate translation of mRNA moieties with reacquisition of control of spine morphology in fragile X.[87] With respect to Down syndrome, overexpression of chromosome 21–derived microRNAs appears to downregulate *MeCP2*, with subsequent decrease in Mef2c and Creb1, all involved in cognitive processing.[88] The potential to regulate genes via microRNA manipulation is well demonstrated in research settings and is being studied with interest for potential therapeutic possibilities.

Stem Cell Therapies

Although stem cell treatment for ID has caught the public imagination, and is offered in unregulated markets, the potential dangers remain unclarified. Additionally, the efficacy of such treatments at present does not match the long-term promise.[89,90] Despite this, there is potential for good. Remarkably, animal studies suggest that the relatively undifferentiated, evolving cortex of neonates and infants may support some ability for structural brain repair as well as cognitive improvement in hypoxic–ischemic damaged mice pups following intranasal mesenchymal stem cell administration.[91,92] Intranasal delivery may also serve as a means to deliver therapeutic molecules.[93,94]

Transgenics

For genetic causes of ID, animal models have repeatedly shown the potential for this treatment. Safety concerns are significant, however,[95] and focus has been on developing safe vectors.[96] Clinical trials are again underway for disorders severe enough to merit the potential risks, including Sanfilippo syndrome type A among others.

Small Molecule Therapies

HISTONE DEACETYLASE INHIBITORS. Histone acetylation appears to be involved in memory formation; its level increases in the brain following learning.[97,98] Many ID disorders associated with deficient memory formation, including Rubinstein–Taybi syndrome (RTS) and fragile X syndrome, show decreased histone acetylation.[99] There are numerous histone deacetylation (HDAC) moieties; this offers an opportunity to target according to need. The potential role is exemplified by a mouse model of RTS via inhibition of targeted HDAC, which restored a range of memory and cognitive functioning deficits in these mice.[100,101] From a preventative perspective, a range of HDAC inhibitors offers promise to protect against cerebral ischemic damage. The potential utility of this applies to neonates as well as older people. Evidence is emerging that HDAC inhibitors provide protection via enhancing angiogenesis, neurogenesis, and neuronal migration.[102] Interestingly, carbon monoxide appears to have a similar role, and has been similarly proposed as a potential therapeutic agent; in both cases, the transcription factor Nrf2 is noted to be increased and is proposed as the mediator.[102,103]

GENTAMICIN/STOP CODON READTHROUGH MOLECULES. For disorders with mutations resulting in premature stop codons, the possibility of suppressing the resultant nonsense-mediated mRNA decay exists. It has been known since 1964 that streptomycin alters ribosomal readthrough of the RNA code.[104] High concentrations of gentamicin and other aminoglycoside antibiotics were shown to bind to eukaryotic rRNA and allow low-frequency readthrough of premature stop codons,[105] precipitating further investigation. An early study suggesting promise in Hurler syndrome noted that there was a small increase in enzyme activity in fibroblast cell lines treated with gentamicin.[106] Attention, however, has largely focused on the role of PTC124, particularly with respect to trials in cystic fibrosis and Duchenne muscular dystrophy.[107] Theoretically, this could be applied to disorder caused by nonsense mutations resulting in premature stop codons, including ID disorders.[108,109] It is to be hoped that, as new premature termination codon (PTC)-skipping compounds are developed, this avenue will evolve, as suggested by animal studies with the aminoglycoside NB84.[110]

STRESS INDUCTION. The stress response of cells across kingdoms is highly conserved, and developed to allow the cell to modulate a series of pathways involving DNA damage, protein stabilization, and energy processing in response to the environment. Disorders involving these pathways may therefore be amenable to therapies that invoke the stress response as a means to circumvent deficiencies. Thus, 4-phenylbutyrate and trichostatin A appear to normalize very long chain fatty acid levels. In a mouse model of X-linked adrenoleukodystrophy, stimulation of both mitochondrial and peroxisomal function via the stress-dependent rather than constitutive pathway offered biochemical circumvention for at least part of the toxic metabolic process.[111]

ELECTROPHYSIOLOGY. Both deep brain stimulation and transcranial magnetic stimulation have been used to treat ID disorders, as well as to treat epilepsy, motor

anomalies, and psychopathology.[112–115] The potential to directly alter regions with aberrant plasticity raises the novel question of whether specific elements of cognitive deficit may be amenable to such therapies in the future.

Summary

We live in an age when the opportunity for treatment of disorders previously thought of as intrinsic and immutable is evolving before us. As this promise is realized, it will herald a new human perspective that no longer accepts as inevitable the consequences of ID. A substantially improved ability to treat cognitive problems would be a breakthrough worthy to join the ranks of such medical revolutions as vaccinations, anesthesia, antisepsis, radiology, and antibiotics. Much work is still to be done, but the tools, understanding, and treatments are emerging in increasingly diverse and unexpected ways.

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Potential Conflicts of Interest

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