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New Innovations: Therapeutic opportunities for Intellectual disabilities

Jonathan D. Picker, MBChB, PhD^{1,2} and Christopher A. Walsh, MD, PhD^{1,3}

¹Division of Genetics, Boston Children's Hospital, Boston, MA, USA

²Department of Pediatrics, Harvard Medical School, Boston, MA, USA

³Department of Medicine, Howard Hughes Medical Institute, Harvard Medical School, Boston, MA, USA

Abstract

Intellectual disability is common and is associated with significant morbidity. Until the latter half of the twentieth 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, 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.

Global significance of intellectual disability

Treatment of intellectual disability (ID) is not a new phenomenon. The earliest references to ID date back to the Papyrus of Thebes, c. 1500 B.C., which included the first identified records reporting disabilities of the mind¹. Societal viewpoints, which have varied widely over time and between different groups^{2,3} largely determine the general response to people with ID, as well as the degree to which society is willing to invest 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 increase⁴. With the realities of de-institutionalization, 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 matters for this group and provide stimulation for research into treatment.

2. Modern understanding of biology

Intellectual disability is not a single entity, it reflects a myriad of different disorders, genetic causes alone may be in the thousands⁵. 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. Intellectual disability, 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 (ICD11) 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: development of the nervous system, and healthy functioning of the neurons and their network. Cognition appears to be particularly dependent upon both the normal synaptic connections, as well as the ability to modulate these connections in response to new stimuli, and adapt as necessary. If the underlying anatomy of the brain is abnormal, for example in a gross brain malformation, (e.g., 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 connectivity¹⁰. However, the majority of genetic causes of ID appear to disrupt the essence of the neuron’s function, namely, its ability to send signals to other neurons that result in an effect. This effect being the strengthening, known as long term potentiation (LTP), or weakening, known as long term depression (LTD), of specific synaptic connections as well as their ability to be further altered to future stimuli¹¹. 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}.

Indeed, the failure of appropriate signaling between neurons across the synaptic junctions of their respective dendritic branches is the central deficit in many cases of ID, as is increasingly apparent as data accrues. 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 dendrites¹⁵. FMRP also regulates translation of these transcripts by inhibition of the mGluR5 glutamate receptor¹⁶. This receptor stimulates sp6 kinase translation for production of necessary proteins to create the neuronal dendritic outgrowths which will interface with other neurons and allow signals to cross between them at the synaptic junction of the dendrites. Normally this process is carefully regulated. In fragile X, the loss of FMRP results in unfettered mGluR5 activity with elevated protein translation^{17–19}. Abnormal protein translation is associated with abnormal dendritic morphology and abnormal patterns of synaptic plasticity, and is associated with the profound effects on the capacity of affected individuals to learn and respond appropriately. An increasing number of genes linked to ID and involving a range of synaptic mechanisms are being identified, whether affecting synaptogenesis directly,^{20; 21, 22–26} or regulating anatomical patterns or consequent functioning^{27, 28}. These pathways offer targeted treatment opportunities that focus on the molecular underpinnings of ID.

3. Currently available therapies

Much of current treatment is focused on environmental optimization. This includes individualized education plans, as well as minimizing complicating co-morbidities (visual, sleep, pain etc.). This approach has provided significant improvements, as exemplified by the improved prognosis for Down syndrome^{29, 30}. Though central to current management; it is not curative.

Specific treatments improving ID at a biological level do exist, and have been around for some time. For example, dietary restriction for newborns identified with PKU, who if left untreated develop an IQ of less than 30, were first attempted by Bickel over 50 years ago³¹. 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 earlier. Examples of prenatal treatments include education and avoidance of neurotoxic compounds such as alcohol or treatment of maternal hypothyroidism³². 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's syndrome, newborn screening offers early diagnosis with the opportunity for meaningful treatment for cognition³⁶. The potential benefit is less clear for disorders for which cognitive treatments are not yet available, such as Rett syndrome³⁷ or fragile X, though other aspects of such disorders may benefit³⁸.

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 cognition³⁹. Interestingly, for previously lethal conditions such as Pompe's disease, in which ERT has changed prognosis, there appears to be intellectual sparing. As glycogen stores accumulate in the brain and the ERT does not cross the blood brain barrier, it was anticipated that, like other storage disorders, cognition would suffer. However, this concern fortunately appears not to have been realized, at least to mid-childhood^{40, 41}. Unfortunately, ERT and metabolic amelioration is often insufficient. Cognitive deficits remain for many metabolic disorders despite treatments. Treatment may exert a partial effect as for some with organic acidemias⁴², but seems less efficacious in other conditions such as tyrosinemia or the urea cycle defects^{43, 44}. Some treatments also aim to improve on existing therapies, such as sapropterin dihydrochloride (BH4) in PKU. While dietary treatment is effective, it is challenging to maintain and compliance falls off over time. This has consequent effects on higher cognitive functions. BH4, a co-factor for Phenylalanine hydroxylase (the defective enzyme in most cases of PKU), has been shown to benefit some patients^{45–47}.

4. 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 result from genetic mutations, and some of these may offer opportunities to directly improve cognition. This method of targeted treatments is currently in trial for a number of disorders. 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 for example, this may not necessarily be the case.

Concern about potential iatrogenic damage to the developing brain of neuroactive treatments needs to be weighed against excess delay where reversibility of the damage may be limited. Choice of timing for treatments will likely be disease specific. However, as research trials work their way down the age spectrum, it is expected that the optimal age for treatment initiation, as well as duration of therapy, will likely become clearer.

Fragile X

Fragile X is the most common inherited cause of ID, affecting 1 in 4000 individuals. As discussed above, the fragile X protein, FMRP, regulates dendritic growth, with the GABAergic system especially sensitive. Lack of FMRP results in unimpeded mGluR5 activity which results in aberrant dendritic development with mis-signalling, resulting in ID, autism and psychopathology⁴⁸. This model offers potential targets. Firstly, GABAergic activity can be increased and indeed the first trial indicating a favorable response using this targeted approach has been carried out using arbaclofen, a GABAB agonist. Initial results in humans suggest improvement in social function and behavior in individuals with fragile X⁴⁹. In addition, mGluR5-specific antagonist trials have commenced (involving AFQ056, RO4917523 and STX107) with a view towards replacing the inhibitory effect of the missing FMRP activity. While definitive data is not yet back, a phase 1 trial of the mGluR5 inhibitor, Fenobam, suggested promising efficacy based on a single dose⁵⁰. Additionally, the antibiotic minocycline, a metalloproteinase inhibitor which appears to inhibit the effect of the mGluR5 receptor, appeared in a double-blind study to have some efficacy^{51, 52}.

MTor pathway

Next to Fragile X, tuberous sclerosis (TS) has probably generated the most activity in the translational research world. Tuberous Sclerosis is a multisystem disorder with significant CNS effects including cognitive deficits. TS is caused by mutations in either TSC1 or TSC2, which encode proteins that form a complex inhibiting activation of mTOR (mammalian Target of Rapamycin)^{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}. A number of 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 compounds⁵⁷. At this time Everolimus, an inhibitor of mTOR, is currently in trial to assess its role in improving the neurocognitive function of individuals with Tuberous sclerosis. 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^{61–63}. This genetic interconnectedness raises some hope that treatments that regulate the MTOR pathway may help at least some other ID/autistic disorders in which the pathway appears to be indirectly perturbed⁴⁸.

Rett syndrome/MeCP2

Rett syndrome is a disorder that occurs mainly in girls and is characterized by regression, ID and distinctive hand movements and caused by mutations in the MeCP2 gene⁶⁴. Milder mutations in MeCP2 cause a variety of other intellectual disability syndromes in both males and females⁶⁵. MeCP2 encodes a protein that binds methylated DNA, and as a regulator of transcription appears to have multiple roles including regulating neural homeostasis genes⁶⁶. In addition it has a role in synaptogenesis, though by as yet unclear mechanisms⁶⁷. 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^{68, 69}. These mouse studies suggested that MeCP2 did 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 deficit⁷⁰. IGF-1, a proxy growth factor with significant molecular and functional overlap with BDNF that crosses the blood brain barrier, offered a potential role in Rett syndrome, since it increased survival and function in the mouse model⁷¹. Following successful phase 1 studies⁷¹, a phase 2 study is underway with cognitive outcome 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, with similar effects but better pharmacokinetic properties, is currently in phase 1 clinical trial^{72–74}.

Trisomy 21/Down syndrome

Trisomy 21 is the most common genetic cause of intellectual disability. 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's disease^{75, 76}, 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. Another study using memantine, a glutamine antagonist, suggested limited cognitive improvement in verbal memory in adults with Down syndrome; however, confirmation is required⁷⁷. 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, previously shown to be associated with neurofibrillary tangles and splicing regulation^{78, 79}.

5. Unmet needs

Three primary areas, remain particularly challenging for development of treatments. These are:

- A. Major congenital structural brain lesions (e.g. holoprosencephaly, hydrocephalus and other lesions impacting gross anatomy)
- B. ID of unknown etiology
- C. Untreated consequences of known disorders, such as neurodegenerative conditions and other causes of neural damage (e.g. 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.

6. Possible new directions for research

Conventional drugs, new uses

As awareness of the underlying neuro-biochemical pathway deficits improve, 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^{80–82}.

MicroRNA

MicroRNAs are a class of noncoding RNAs that bind to mRNA and regulate their translation. Over half of MicroRNAs are neurally expressed⁸³. Many appear to have broad regulatory roles in cognitive processes including regulation of neuroplasticity⁸⁴; regulating protein levels (e.g. BDNF and the NMDA receptor NR2A in ID disorders⁸⁵) and may function as intermediate molecules in regulatory functioning of critical genes such as MeCP2 in Rett syndrome⁸⁶ or for FMRP in controlling dendritic spine morphology in

animal models of fragile X⁸⁷. Indeed, therapeutic microRNAs, acting at the ribosome, may inhibit indiscriminate translation of mRNA moieties with re-acquisition of control of spine morphology in fragile X⁸⁸. 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 processing⁸⁹. The potential to regulate genes via miRNA manipulation is well demonstrated in research settings and is being studied with interest for potential therapeutic possibilities.

Stem cell therapies

While stem cell treatment for ID has caught public imagination, and is offered in unregulated markets, the potential dangers remain unclarified. Additionally, the efficacy of such treatments at present does not yet match the long-term promise^{90, 91}. 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^{92, 93}. Intranasal delivery may also serve as a means to deliver of therapeutic molecules^{94, 95}.

Transgenics

For genetic causes of ID, animal models have repeatedly shown the potential for this treatment. Safety concerns are significant however⁹⁶ and focus has been on developing safe vectors⁹⁷. Clinical trials are again underway for disorders severe enough to merit the potential risks, including Sanfilippo type A amongst others.

Small molecule therapies

Histone deacetylase inhibitors—Histone acetylation appears to be involved in memory formation; its level increases in the brain following learning^{98, 99}. Many ID disorders associated with deficient memory formation, including Rubinstein Taybi syndrome (RTS) and fragile X syndrome show decreased histone acetylation¹⁰⁰. There are numerous histone deacetylation (HDAC) moieties; this offers an opportunity to target to the need. The potential role is exemplified by a mouse model of RTS via inhibition of targeted HDAC, which restored a range a memory and cognitive functioning deficits in these mice^{101, 102}. From a preventative perspective, a range of HDAC inhibitors offer 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 migration¹⁰³. 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^{103, 104}.

Gentamicin/stop codon read-through 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 altered ribosomal read-through of the RNA code¹⁰⁵. High concentrations of gentamicin and other aminoglycoside antibiotics were shown to bind to eukaryotic rRNA and allow low frequency read-through of premature stop codons¹⁰⁶ 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 gentamicin¹⁰⁷. Attention, however, has largely focused on the role of PTC124, particularly with respect to trials in cystic fibrosis and Duchenne muscular dystrophy¹⁰⁸. Theoretically, this works for any disorder caused by nonsense mutations resulting in premature stop codons including ID disorders^{109, 110}. 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 NB84¹¹¹.

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 to the environment. Disorders involving these pathways may therefore be amenable to therapies that invoke the stress response as a means to circumvent or enhance 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 process¹¹².

Electrophysiology—Both deep brain stimulation and transcranial magnetic stimulation have been used to ID disorders, as well as to treat epilepsy, motor anomalies, and psychopathology^{113–116}. 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 where the opportunity for treatment of disorders previously thought of as intrinsic to the affected person 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, antiseptics, anesthesia, radiology, antibiotics, dialysis, and organ transplantation. Much work is still to be done, but the tools, understanding, and treatments are becoming available in increasingly diverse and unexpected ways.

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Figure 1.
Targeted drug trials in sp6kinase upstream pathways
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 towards clinical trials