Integrative Molecular Medicine

Short Communication ISSN: 2056-6360

Gene therapy and CNS infant hypotonia

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Abstract

Gene therapy is increasingly proposed for treating central nervous system disorders, including therapeutic intervention for fetal hypotonia. Current genetic and molecular methodologies have streamlined diagnostic algorithms, significantly advancing the resolution of this challenging spectrum of etiological abnormalities and encouraging their appropriation for therapy. Prospects for gene therapy as a standalone treatment, however, are complicated by the complex neural architecture formed during development that will likely require intervention limited to discrete synaptogenic intervals.

Introduction

Interest in gene therapy has had, by the standards of its technical evolution, a long history. As early as 1972, four years after the official date for the cracking of the genetic code, researchers first suggested its use for genetic diseases in the journal Science, and in 1990, a four-year-old girl with severe immunodeficiency became the first patient to be treated with gene therapy. Through dedicated research efforts since, many challenges to its implementation have been addressed and some have been overcome [1]. The development of a gene therapy product in 2000, for example, testifies to the commercial recognition of this success. Recently, it has been proposed for use in treating nervous system diseases.

This latter is good news for a range of etiologies that induce chronic impairments seen in infants. Among these are infant hypotonia, colloquially termed floppy infant syndrome. Infant hypotonia comprises a broad spectrum of etiological abnormalities that are historically notorious for posing diagnostic challenge. Their symptoms are characterized by a generalized loss of muscle tone, which are displayed in a variety of clinical conditions. Diagnosis is considerably exacerbated, moreover, by the absence of biomarkers and nosological dependence [2]. Presenting symptoms like weak posture, excessive joint range, and the inability to resist slight pressure accordingly are potentially due to many causes seen in the somatic expression of infant neurological diseases [3]. M Iraschi's diagnostic algorithm, for example, is notable for the assessment range that may be tasked prior to reaching a conclusion. [4].

The prospective use of gene therapy in infant hypotonia is fueled by recent diagnostic successes related to the rapid expansion of molecular genetic diagnostic methods, now routinely used in hypotonia assays. Among other proponents, Paul Fisher of Stanford's Department of Neurology and Pediatrics, recently advanced the claim, recently advanced the claim that therapeutic resolution of fetal hypotonia is an achievable objective [5]. In his view much of the newly inspired therapeutic promise relates directly to the convertibility of these rapidly expanding methods for therapy.

This positive perspective on diagnosis is supported by the current array of diagnostic assays [6]. Together with clinically based evaluative protocols, like spinal muscular atrophy in combination with electromyography, these are promising for their rapidity and specificity. Comparative genomic hybridization with various restriction endonuclease cocktails, for example, offers an especially powerful method for detecting very low levels of sequence variation, and is currently replacing more traditional cytogenetic assays.

The prospect of successfully appropriating similar methodologies for correcting defective coding sequences for the purpose of therapy reflects a broader interest in the technology. Indeed, similar proposals propelled the convening of the national convocation in Washington DC in December of 2015, headed by David Baltimore, concerned with the potential promise, but also the danger, of implementing CRISPR technology [7]. Expressed concerns relate to gene therapy's theoretical potential to 'permanently' alter either genetic instructions or to correct coding defects by inserting or otherwise introducing sequences that yield novel gene products. With the generation of a correctly restored protein or peptide product, or the prevention of undesirable ones through techniques like missense or reverse RNA that block translation, outcomes are thereby directly related to the functional adequacy of the corrected product, which could carry out new cellular roles.

The potential for modifying biochemical machinery, in fact, has been the basis for investigations into the efficacy of gene therapy to treat human disease for over two decades now [1]. This conception of therapy through molecular adequacy has been appropriated for gene therapy in nerve tissue also. Chief obstacles, accordingly, have been identified with accessing the genetic machinery used for repairing protein products or the molecular mechanisms of production. Varied issues include availing type specific tissue, crossing the blood brain barrier, and stimulating transcription with DNA promoters.

Recent progress in methods to access nervous system tissue, especially, includes significant advances in the engineering of viral delivery vehicles and synthetic Nano particles. Foust et al, for example, reported that AAV serotype 9 (AAV9) was able to traverse the blood brain

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Received: August 06, 2018; **Accepted:** August 15, 2018; **Published:** August 20, 2018

barrier, and yield widespread, though variable transgene expression in both astrocytic and neuronal cells [8]. The current list of viral vectors that could be used for therapy is extensive, with their potential further amplified by a variety of genetic engineering procedures that can modify discrete bases or large modular sequences. Unlike viral vectors, on the other hand, non-viral, nanoparticles lack biomolecular modalities that have been evolutionarily refined for uptake in the nervous system. However, they are potentially amenable to a much broader range of synthetic alterations, making them, in many instances, a preferred mode of transport. Nanoparticles notably can be made from a variety of molecular compounds and their morphologies can assume a much broader range of configurations, including liposomes, nanotubes, and magnetic nanoparticles [9,10].

Given the many etiologies that give rise to hypotonia symptoms, however, the specific premise of molecular adequacy for therapy may be unlikely to yield a broad, stand-alone approach to therapeutic intervention; indeed, in many cases it is likely to be insufficient. Among the loci that contribute to hypotonia symptoms, for instance, are included muscle (congenital myotonic dystrophy), neuromuscular junction (congenital myasthenia gravis), motor nerve (hypo myelinating neuropathy), motor soma of the spinal cord (spinal muscular atrophy), and brain tissue (cerebral dysgenesis and metabolic diseases), clearly, a functionally and anatomically diverse set of tissues. Gene therapy approaches, by contrast, are more likely to be suited to applications where tissue type is relatively uniform and where the expression of the gene product has a direct bearing on physiological function. Such considerations favor applications that are more distally localized with respect to a brain-based origin, that is, more likely to be successful in muscle masses, myelinating nerve segments, and at motor synaptic junctions.

Less likely to be successfully treated by gene therapy alone are the many genetic impairments affecting brain tissue, which are estimated to comprise nearly 70 percent of all diagnosed cases of hypotonia [3]. Intervention in these circumstances must confront the functional complexity of neural tissue that critically depends on correctly forming synaptic connections. The anatomical and physiological complexity of brain tissue is illustrated, for example, by one of the signal discoveries of early neuroscientific research, which revealed the critical dependence of structuring network circuits on sensorial activity [11]. In an early and telling observation, Wiesel and Hubel showed that cats could become permanently blind if they were deprived of light stimulation during a critical window when the cortical visual networks were being formed. Restoring activity after this period was incapable of reversing the effect. That is, once the synaptic contacts and network processes had been established molding influences were no longer effective in modifying the synaptic connections in the occipital cortex; the animals, therefore, were permanently blind due to the presence of a brain rather than a retinal lesion. Intuitively, this can be understood to be due to the highly complex, three-dimensional anatomy of networks formed under the influence of sensorial activity, which works in concert with developmental processes to yield a functional synaptic order. Such architectures, moreover, are dominated by complex recurrent connections where reciprocal inhibitory and excitatory innervation dictates the generation of non-linear, dynamical physiologies characteristic of brain neural activity, known as attractors. Without evoking concurrent developmental or translational machineries the ability to restore these unique activity forms by situating corrected gene products to these loci is compromised and unlikely to reverse the effects of deprivation by reliance on therapies premised only on molecular adequacy.

Moreover, this is not an obstacle posed during development only, but a feature that persists throughout a lifespan due to the plasticity of brain activity. Navigational exploration, for example, elicits experience dependent multimodal sensorial activity that is captured in the grid and place cells of the hippocampus [12]. To overcome these hurdles gene therapy will likely require a symbiosis with supplemental approaches that account for developmental or experiential variation during synaptogenic epochs.

Accordingly, developing such prospective options will likely need early or prior genetic diagnosis of the specific class of hypotonia as well as key information on the temporal sequencing of processes critical to establishing synaptic connectivity. The appearance in early infancy of CNS hypotonia suggests that underlying the impairment of central nervous system networks are targeting or synaptogenic errors during major formative epochs, that is, during critical windows when synaptic connections for principal brain networks are structured [13]. These heightened periods of plasticity entail numerous interacting factors, including variation in genetic expression, responsivity to developmental cues, and enhanced sensitivity to environmental input, usually in the form of stimulus evoked activity [14]. As critical periods of development, these also constitute periods of increased vulnerability, when influencing factors may be less than optimal, or mis assimilated, leading to neurodevelopmental disorders [15]. Conversely, they are also likely to constitute intervals when genetically introduced variation may be more accessible as a therapeutic strategy. Major periods are now known to encompass synaptogenesis in the brain stem (early), thalamus (intermediate), and cortical zones including the cerebellum (late). In the case of Prader Willi syndrome (PWS), for example, the displacement of cortical recovery resembles the time evolution of hypotonia that is seen in PWS patients, consistent with postulates that link PWS etiology to an impact on cortical synaptogenesis occurring during this phase. Hence, identifying the phase will likely assist in determining the timing of therapy as well as in targeting the spatial origin of the disease.

Among a number of CNS impairments, moreover, synaptogenic phases are characterized by a delay, which is then followed by a partial and permanent phase of recovery [15]. These observations suggest that such impairments, in fact, may be focal, with a number of synaptogenic mechanisms remaining intact and so zones where prospective therapy could be successfully applied. Coupled with a burgeoning knowledge on the mechanisms underlying cortical motor processes the targeting of affected mechanisms can be further refined. The transient symptoms of PWS hypotonia, for example, are noted for their universality suggesting impacts on global and/or primitive functions that are coupled to fundamental physical features like space and time [16]. The central origin of the etiology and the breadth of the tonic responses impacted, in fact, are telling signatures leading to the conclusion that PWS hypotonia involves aberrant activity across distributed cortical networks period; Hence likely to involve processing primitives coordinating spatiotemporal features of motor movement originating in foci of the cerebellum or motor planning processes that frame intentional movement to the whole individual, which are localized to the default mode network [16-18].

Conclusion

Proposals for gene therapy in central nervous system tissue have attained significant successes in delivery vehicles that target specific neural domains. However, the complex synaptic connectivities structured during developmental and experiential modifications are

unlikely to be resolved by therapeutic strategies premised on modified gene products only. Such complex scenarios as CNS fetal hypotonia will likely entail multiple hybrid approaches that are synchronized with synaptogenic phases.

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