Drug Discovery Research for Hydrocephalus

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EDITORIAL

In 2013, clinical and basic science research has rolled the dice further to extend our understanding to hydrocephalus. A group of research team at Boston Children’s Hospital and Harvard Medical School, led by neurosurgeon, Joseph Madsen, has published the laboratory investigation results on vascular endothelial growth factor, VEGF, and showed its potential effect on the development of experimental ventriculomegaly in an animal model [1]. Ventriculomegaly, the dilatation of the lateral ventricles is one of the diagnostic criteria for hydrocephalus. Hydrocephalus, water in the head problem, is a neurological condition characterized by accumulation of fluid in the cerebral ventricles. The current treatment is either ventriculostomy or shunt surgery to drain excessive fluid. However, shunt surgery often requires additional intervention due to functional failure. Concern over pediatric patients with hydrocephalus managed successfully by shunt, say, for 10 years without revision, is the fact that anatomy surrounding the shunt changes with growth, while shunt is not designed so. Adaptation to altered anatomy can affect physiology and shunt function. The risk for young patients is the shunt malfunction and resulting complications. For this reason, a non-surgical approach that may lessen this difficulty in the future is necessary. Pharmacological approach alone, however, can also potentiate an adverse effect. How we manage this condition with currently available surgical and potential non-surgical approach might be, therefore, the key to success. In doing so, drug discovery and testing candidate molecules in animal models for achieving this purpose can enhance the quality of clinical decision-making at the end.

Potential drug research for hydrocephalus

By far, different targeting strategy has been taken, suggesting potential drug treatment or pharmacological treatment in combination with shunt surgery [1] for hydrocephalus (Table 1). One of the known experimental hydrocephalus is studied using kaolin-injected animal model. Since cerebral cortex was severely compressed in kaolin-induced hydrocephalus [2], it was hypothesized that movement of extracellular substance is impaired. Using kaolin injection, it has been shown that compositional change in extracellular constituents such as decorin was negligible [3]. Fibrosis resulting from TGFβ1 upregulation in the kaolin-induced hydrocephalus was suggested as target to suppress. In recent seminal work from the U. K. researchers, decorin, a small extracellular matrix proteoglycan, has been shown to prevent juvenile communicating hydrocephalus [4]. To mitigate fibrosis in post-hemorrhagic hydrocephalus, hepatocyte growth factor, HGF, also known as scatter factor has been used in an animal model of intrathecal TGFβ1 [5]. Using in utero injection of lysophosphatidic acid, LPA, an antagonist for LPA receptors, Ki16425, has been exhibited to prevent fetal hydrocephalus [6]. Angiogenic factors and their inhibitors have been demonstrated to play a preventive role in animal models of fetal and pediatric hydrocephalus. Bevacizumab [7], a monoclonal antibody known to inhibit all isoforms of human VEGF-A has been co-infused at ng/ml concentration with VEGF-A165. The result demonstrated prevention of ventriculomegaly and ependymal alteration readily seen in the VEGF-infusion alone [8]. Celecoxib, when used alone or administered along with ZD6474, VEGFR2 inhibitor, have rescued the previously observed pathology in a premature infant model of hydrocephalus following hemorrhage [9]. For experimental hydrocephalus resulting from posterior obliteration such as aqueductal stenosis and maldeveloped subcomissural organ, targeting reactive astrocytosis and aberrant G protein coupled receptor, GPCR, signaling by astrocytes were deemed pivotal. In this model of obstructive hydrocephalus, Minocycline [10] and Doxycycline [9] were shown to reduce glial scar and to prevent induction of hydrocephalus, respectively. In the latter model, however, care should be taken, as the phenotype of genetic mutants was inducible through the exogenous provision of doxycycline. Doxycycline was implemented to control level of expression in target gene, but aimed to suppress neither angiogenesis nor MMP-9, as in other pathologic conditions [10]. Nevertheless ‘Ro1 animals’ are one of the experimental models appeared to demonstrate the precise controllability of the hydrocephalic phenotype depending on the concentration of doxycycline. Whether or not, however, this model represents communicating or obstructive hydrocephalus is unclear because of the contradictory descriptions [9, 11]. In a ciliopathy mutant model of Bardet-Biedl Syndrome, receptor for platelet-derived growth factor, PDGFRα, was targeted in order to mitigate the pathologic outcome. Strikingly, it has been reported that targeting this pathway with lithium rescued neural progenitor cell proliferation in the mutant animals, suppressing the dilatation of the ventricular size [12]. In an experimental ventriculomegaly with neurodegeneration due to senescence, targeting the mammalian target of rapamycin, mTOR, has shown an anti-aging effect in OXYS rats, a laboratory breed engineered to show accelerated aging with higher levels of oxidative free

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Submitted: 19 December 2013
Accepted: 12 January 2014
Published: 16 January 2014

Table 1: Preclinical research aiming at drug treatment for hydrocephalus.

<table>
<thead>
<tr>
<th>Target</th>
<th>Animal model</th>
<th>Evidence</th>
<th>Associated disease; Treatment</th>
<th>Age</th>
<th>References</th>
</tr>
</thead>
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<tr>
<td>VEGF</td>
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<td>Ventriculomegaly</td>
<td>Hydrocephalus; Bevacizumab</td>
<td>Adult</td>
<td>[18]</td>
</tr>
<tr>
<td>COX2; VEGFR2</td>
<td>Glycerol injection</td>
<td>Ventriculomegaly; Elevated VEGF</td>
<td>GMH; PIHC; Celecoxib and ZD6474</td>
<td>Fetal</td>
<td>[7]</td>
</tr>
<tr>
<td>PDGFRA</td>
<td>A ciliopathy mutant</td>
<td>Ventriculomegaly; Impaired CSPG4*</td>
<td>Bardet-Biedl Syndrome; Lithium</td>
<td>Neonatal</td>
<td>[12]</td>
</tr>
<tr>
<td>TGFβ1</td>
<td>Kaolin injection</td>
<td>Ventriculomegaly; Fibrosis</td>
<td>PHHC; Decorin**</td>
<td>Juvenile</td>
<td>4</td>
</tr>
<tr>
<td>TGFβ1</td>
<td>TGFβ1 injection</td>
<td>Ventriculomegaly; Fibrosis</td>
<td>PHHC; HGF</td>
<td>Neonatal</td>
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<tr>
<td>LPA</td>
<td>In utero injection</td>
<td>Ventriculomegaly; Hemorrhage</td>
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<td>Gliosis</td>
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<td>Ventriculomegaly; Reactive gliosis</td>
<td>Aqueductal stenosis; Minocycline</td>
<td>Juvenile</td>
<td>8</td>
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<tr>
<td>G(i)-coupled RASSL Ro1</td>
<td>Genetic; tet inducible</td>
<td>Ventriculomegaly; Altered SCO</td>
<td>Ventriculomegaly; Doxycycline</td>
<td>Adult</td>
<td>9, 11</td>
</tr>
</tbody>
</table>

*CSPG4: Chondroitin Sulfate Proteoglycan 4; ** Decorin: A small cellular or extracellular matrix proteoglycan; SCO: subcommissural organ; VEGF: vascular endothelial growth factor; COX2: cytochrome c oxidase subunit II; TGFβ1: transforming growth factor 1; LPA: Lysophosphatidic Acid; GMH: germinal matrix hemorrhage; PIHC: post hemorrhagic hydrocephalus; HGF: hepatocyte growth factor; H-Tx rats: hydrocephalic Texas rats; VEGFR2: vascular endothelial growth factor receptor 2; PDGFα: platelet growth factor receptor α; tet: tetracycline; RASSL: receptor activated solely by synthetic ligand

ACKNOWLEDGEMENTS

The work is dedicated to the late Dr. M. Judah Folkman for his insight and encouragement. J. W. S. is a recipient of the inaugural MYI award from the Hydrocephalus Association.

REFERENCES


Cite this article