Exploring and translating novel approaches targeting the choroid plexus for the treatment of hydrocephalus: where are we now?

Olivier Sluijters MRCS[1], John Pooley PhD[2], Will Singleton FRCS PhD[2,3]

[1]Department of neurosurgery, North Bristol NHS Trust
[2]Bristol Medical School, University of Bristol
[3]Department of neurosurgery, Bristol Royal Hospital for Children

Olivier J.J. Sluijters

ST3 Neurosurgery, Severn

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Abstract

Hydrocephalus is common with a mixed phenotype and aetiology. Its treatment is predominantly surgical, with temporary or permanent cerebrospinal fluid (CSF) diversion, which does not address the underlying disease mechanism.

The choroid plexus (ChP), a secretory epithelium found in all four ventricles of the brain, produces most CSF within the central nervous system and has been investigated extensively over the past century to understand its function and potential role as a therapeutic target. Past attempts at either medically or surgically controlling its rate of secretion have not significantly altered our approach to the treatment of hydrocephalus, with CSF diversion remaining the main intervention.

Rodent models of post-haemorrhagic hydrocephalus (PHH) have advanced our understanding of choroid plexus function in health and disease. Pre-clinical experiments have demonstrated a hypersecretory response in the ChP that may contribute to PHH. Targeting the choroid plexus directly may therefor present a novel therapeutic method. These findings have led to a significant increase in pre-clinical studies exploring this hypersecretory response and how to modulate it. Translating these promising results to clinical practice will rely on the development of large animal hydrocephalus models, which thus far has been limited.

This literature review discusses the recent advances in targeting the ChP as a treatment for hydrocephalus, both surgically and non-surgically, and the current barriers to further advancement of this approach.

Introduction

Cerebrospinal fluid (CSF), which Cushing described as 'the peculiar watery medium which bathes the central nervous system'[1], plays a crucial role in the central nervous system (CNS). It aids development, provides protection, buoyancy, homeostasis of the ionic environment, nutrient supply and a pathway for waste clearance[2,3]. It is predominantly produced by the choroid plexus (ChP), with extra-choroidal contributions from the ependyma and blood-brain barrier (BBB) suggested[4,5]. It circulates through ventricular, cisternal, subarachnoid and glymphatic pathways[6,7], propelled by a combination of hydrostatic pressure, arterial pulsations, respiratory patterns and beating of cilia. Its absorption takes place in arachnoid granulations, nerve sheaths, dural lymphatics[8] and other regions[9]. The production, circulation and absorption of CSF is a rapidly evolving field of research, and traditional hypotheses are continuously challenged[10].

An abnormal accumulation of CSF in the ventricles leads to *hydrocephalus*. It can be defined as 'a clinical and neuroradiographic diagnosis characterised by an abnormal accumulation of CSF which can occur in conjunction with, or in absence of, changes to intracranial pressure'[11]. The clinical presentation can be highly variable, ranging from the acutely comatose patient to a subtle cognitive decline. It is a highly prevalent condition, affecting patients of all ages[12–14] and the morbidity, mortality and economic cost associated with it is significant[15,16], as emphasised by those trialling novel treatments[17]. It was originally subdivided into being caused by overproduction of CSF, a blockage of its circulation or an impaired re-absorption of CSF. It is now known that these processes frequently co-exist.

Many non-surgical therapies have been investigated and trialled over the past century[18], however the mainstay of hydrocephalus treatment remains surgical and is based on CSF diversion, as medical treatment is often temporary and limited by significant side-effects, such as acetazolamide[18]. The inherently imperfect nature of CSF diversion, which does not always address the root cause of hydrocephalus, means that patients are plagued by complications and lifelong follow-up requirements[16,19].

Some of the promising advances in this field have targeted the ChP directly. Considering recent evidence that the ChP demonstrates a hypersecretory response in post-haemorrhagic and post-infectious hydrocephalus[20], there is a growing interest in targeting it directly to reduce the need for permanent CSF diversion. This essay will discuss the latest surgical and non-surgical advances in targeting the ChP directly for the treatment of hydrocephalus and highlight areas of novel research with translational potential.

The choroid plexus

Structure and development

The ChP is a secretory epithelium found on the floor of both lateral ventricles and the roof of both 3rd and 4th ventricle, with a rich blood supply from multiple choroidal arteries. Initial ventricular expansion during embryonic development occurs before the ChP appears[21], so the role of CSF production is likely initially carried out by neuroepithelium and later taken over by the choroid plexus epithelium.

The ChP consists of a single layer of cuboidal epithelial cells[22] which are tightly interlinked with a range of junctional proteins (figure 1)[23,24], supported by a basement membrane and a rich network of fenestrated capillaries, with surrounding stromal cells and fibroblasts[22,25]. These cellular layers combined form the blood-CSF barrier (BCSFB)[26], which is a far more restrictive barrier than the ventricular ependyma. Choroid plexus epithelial cells display multiple features that align with their function of CSF production, such as microvilli, a basolateral border with interdigitations, high density of mitochondria[27], high expression of sodium-potassium ATPases (N-KA)[28] and membrane transport proteins[29]. The surface area of the ChP is 2 – 5 m^2, approximately half the blood-brain-barrier surface (10m^2)[30]. These anatomical and microscopic features of the ChP support its function as a highly active secretory unit.

CSF production in the choroid plexus

CSF production is estimated at around 500ml/day in the average adult, with 80-90% produced by the ChP[5,31]. Whilst there is ongoing debate on this matter, there is a large body of evidence supporting the contribution of the ChP in CSF production[26,32]. These include key animal studies by Dandy[33] , Rougemont[34] , Welch[35–37] , Ames [38] and Pappenheimer[39,40] . Some argue against a significant contribution of the ChP[41,42] and these discussions are covered in detail in several reviews[5] but are beyond the scope of this essay.

Numerous transporter molecules and ion channels have been identified in the choroid plexus, the experimental evidence basis for which has been covered in several reviews[4,5,26,30] . The currently known key molecular structures are summarised in figure 1 with their associated ion movements. The method by which the ChP transports fluid, against an osmotic gradient, remains undetermined, with several possible theories[5,26,32] .

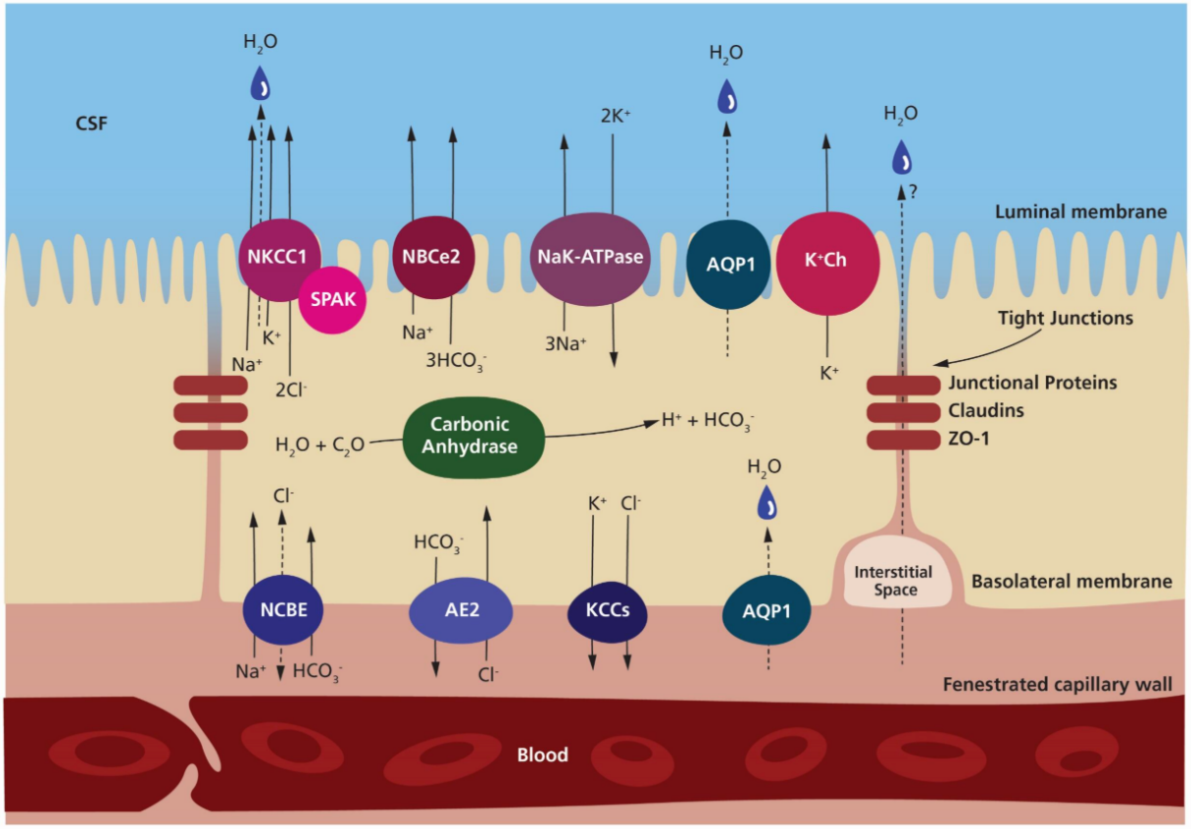

Figure 1: *Overview of key structural and transporter molecules in the choroid plexus epithelium with the associated direction of ion and water movement. The luminal surface of the choroid plexus epithelial cell has microvilli to expand its surface area. The junctions between cells are formed by junctional proteins, such as claudins and ZO-1. There are pockets of interstitial space on the basolateral side, where the basement membrane and fenestrated capillary wall forms the remainder of the blood – CSF barrier. The main transport molecules on the luminal side are cation-chloride co-transporters (NKCC1), sodium-potassium ATPase (NaK ATPase), aquaporin 1 channels (AQP1), sodium-bicarbonate co-transporter (NBCe2) and potassium channels (K+Ch). SPAK (STE20/SPS1-related Proline-Alanine-rich Kinase) is closely associated with NKCC1 and phosphorylates the transporter, promoting its activity. On the basolateral side, the main transport molecules are sodium driven chloride-bicarbonate exchangers (NCBE), anion exchangers (AE2) and other cation cotransporters (KCCs). Carbonic anhydrase (CA) is found within the cytoplasm and catalyses the conversion of H2O and CO2 into HCO3- and H+, which is a key step in facilitating ion fluxes and fluid transport across the epithelium. Various experimental studies with knockout rodent models, topically and systemically applied inhibitors have demonstrated the existence of these molecules and their impact on CSF production, although the nature of their interactions remains unclear.*

Surgical targets

Endoscopic choroid plexus coagulation

Since L'Espinasse, a urologist, first demonstrated an endoscopic method to coagulate the ChP in 1910, multiple series and trials have been done to investigate its effectiveness. In 1986 Griffith and Syman published a series of 70 cases of paediatric hydrocephalus demonstrating that choroid plexus coagulation (CPC) led to 30-49% shunt-independence[43] and a later series of ventricular perfusion protocol combined with CPC[44] which led to a 52% shunt-independence rate. The rationale was that the breakdown products from coagulating the ChP may affect subsequent absorption of CSF.

CPC has had a resurgence of use since the early 2000s in conjunction with endoscopic third ventriculostomies (ETV). Multiple series have been published comparing ETV and ETV combined with CPC[45–48]. A systematic review highlighted a reduction in failure rates (i.e. need to place a ventriculoperitoneal shunt) in ETV + CPC cohorts compared to ETV alone across 3 studies (quoted failure rates of 0.33, 0.42 and 0.29 for ETV + CPC versus 0.46, 0.57 and 0.75 for ETV)[49]. It is evident from the varying rates across studies that patient selection, surgical technique and healthcare setting have a significant impact. Failure rates were higher in high-income countries than LMICs, which may be attributable to different underlying disease processes. A large cohort study of 348 children demonstrated that regardless of aetiology, ETV + CPC results in higher success rates than the ETV success score predicts (66.9% success at 6 months, vs 45.4% predicted), reaffirming the added value of CPC[50]. The ESTHI trial (NCT04177914) is a current multi-centre RCT comparing ETV with ETV + CPC and is due to complete in 2027.

A retrospective study of 68 patients undergoing functional hemispherectomies for intractable epilepsy with one group having additional open CPC, demonstrated that this addition reduced rates of ventriculoperitoneal shunt insertion (7.7% in CPC group vs 28.7% in no CPC group)[51]. Similarly promising results were achieved in a small series of patients with hydranencephaly, where choroid plexectomy led to lower rates of CSF diversion[52].

Choroid plexus destruction by other means

Other methods that have been trialled to reduce CSF production from the ChP by destroying its tissue include the use of gold, rhenium and technetium[53–57], which were initially promising but proved unsuccessful in animal models of kaolin-induced hydrocephalus.

Stereotactic radiosurgery is used to target neoplasms of the ChP, both primary and metastatic, and work has been done detailing the dose requirements to achieve sustained cell death in normal ChP tissue[58]. There are no published works yet trialling this with the primary aim of treating hydrocephalus.

Embolisation of the distal anterior choroidal arteries has been described in a case report of a child with diffuse villous hyperplasia of ChP, whose CSF production remained at 800-1000ml/day despite CPC and medical management – they developed ascites after a VP shunt[59]. After bilateral anterior choroidal artery embolisation, CSF production declined to 200-

300ml/day, though this did lead to a silent posteromedial thalamic infarct. There have been no other reports of this approach in the literature, except in pre-operative settings for the resection of ChP tumours[60,61], or treatment of vascular malformations, which highlight the variable vascular anatomy[62].

Indirect approaches

A combination of CSF 'washout' and fibrinolytic agents have also been trialled to prevent PHH, but these treatments do not directly target the ChP, though an indirect effect should be considered. The DRIFT trial demonstrated improved cognitive outcomes at 10 years and demonstrated the socio-economic impact[17] and both ELVIS and EARLYDRAIN trials support aggressive CSF diversion after haemorrhage to reduce the haemorrhagic and inflammatory load within the CSF circulation[63,64]. Notable ongoing research efforts include the ENLIVEN-UK trial, a RCT investigating a standardised protocol for neuro-endoscopic lavage.

Molecular targets to alter choroid plexus function

Several molecular targets in the ChP that can be used to modulate its activity, have recently been discovered in rodent models. Key agents and pathways have been summarised in *figure 2, figure 3, figure 4* and *figure 5* and are discussed below.

The inflammation pathway: TLR4-SPAK-pNKCC1

NKCC1, a Na+/K+/2Cl- cotransporter, present on the luminal side of choroid plexus epithelial cells, plays an important role in CSF production. Its exact nature, in both normal and pathological conditions, remains unclear. The use of intraventricular furosemide and bumetanide, which selectively block this channel, lowered CSF production in the ChP[65,66], and this has been repeated in more recent experiments[67–71][72] but there is ongoing debate as to whether its transport direction is predominantly inward or outward[5,73]. It is also unclear whether NKCC1 contributes to an osmotic gradient[5,72] or directly transports H2O molecules[73–77], with evidence in favour and against both theories.

NKCC1 is crucial in current research into inflammatory pathways driving CSF hypersecretion. This was highlighted by Karimy[67] in their mouse model of PHH. Through stepwise inhibition and direct measurements of CSF production, they showed a clear upregulation of inflammatory pathways after intraventricular haemorrhage, involving TLR4, NFκB and SPAK. SPAK is key in phosphorylation of NKCC1, which drives its activity[78–80]. Selective inhibition of components of the pathway (figure 1) attenuated the hydrocephalus and CSF hypersecretion that was present in the untreated mice with IVH. Not only has this model suggested several promising pharmacological targets, but it also challenges the longstanding belief that PHH is predominantly caused by CSF malabsorption.

A SPAK inhibitor, ZT-1a, was developed which was effective in reducing post-haemorrhagic CSF hypersecretion[68] when administered intraventricularly in rats. It inhibits WNK/SPAK/OSR1 mediated phosphorylation of NKCC1, as well as other cation/Cl- cotransporters. Notably, it is effective in ischaemic stroke models when given systemically, presumably due to localised breakdown of the BBB, where it reduces oedema, infarct size and improves neurological outcomes[68].

The evidence supporting NKCC1's central role in CSF secretion and its potential as a target is further strengthened by mouse models with genetic knockout of either AQP1 or NKCC1, as well as viral choroid plexus-specific knockdown of either channel. AQP1 function did not significantly contribute to CSF production, but NKCC1 function did, with a 40% reduction when knocked down[81] .

There is growing evidence that PHH and post-infectious hydrocephalus (PIH) are both forms of acquired inflammatory hydrocephalus[20]. There is significant overlap between their inflammatory cascades, and a possible target is the PI3K/Akt/mTOR pathway, which drives SPAK activation[82]. Rapamycin, an mTOR inhibitor, delivered systemically, attenuated CSF hypersecretion in rodent models of both pathologies, supporting this theory. Rapamycin has been used effectively in the treatment of advanced cancers, renal transplant rejection and

tuberous sclerosis. This makes it a viable candidate for further research, but caution is advised in presuming the mechanism of action in hydrocephalus, as it has such wide-ranging effects[83].

The inflammatory cascade that lies downstream of TLR4, specifically the MyD88-dependent pathway that drives the production of pro-inflammatory cytokines[84], provides many more possible targets for pharmacological inhibition, and is not necessarily limited to CSF hypersecretion in hydrocephalus[85].

Not all evidence points towards inhibition of NKCC1 however, lest we assume this is the obvious solution. In a mouse model of both kaolin-induced obstructive hydrocephalus[86] and PHH[87], adeno-associated virus (AAV) induced overexpression of NKCC1 on the luminal surface of ChP epithelium was effective in mitigating ventriculomegaly and increased CSF clearance[87]. The authors theorise that the ChP relies on phosphorylating NKCC1 to enhance CSF clearance through absorption, possibly triggered by raised extracellular K+. The actions of NKCC1 in this context are therefore strengthened through AAV-overexpression. They also highlight that the natural decline in CSF [K+] in early postnatal development coincides with the GABA-switch, where GABA's role changes from excitatory in early cortical progenitor cells to its classical inhibitory role[88], which is closely related to ion concentrations in the interstitium[89]. Any intervention that interferes with this process has the potential to exacerbate or alleviate several neurodevelopmental disorders[90].

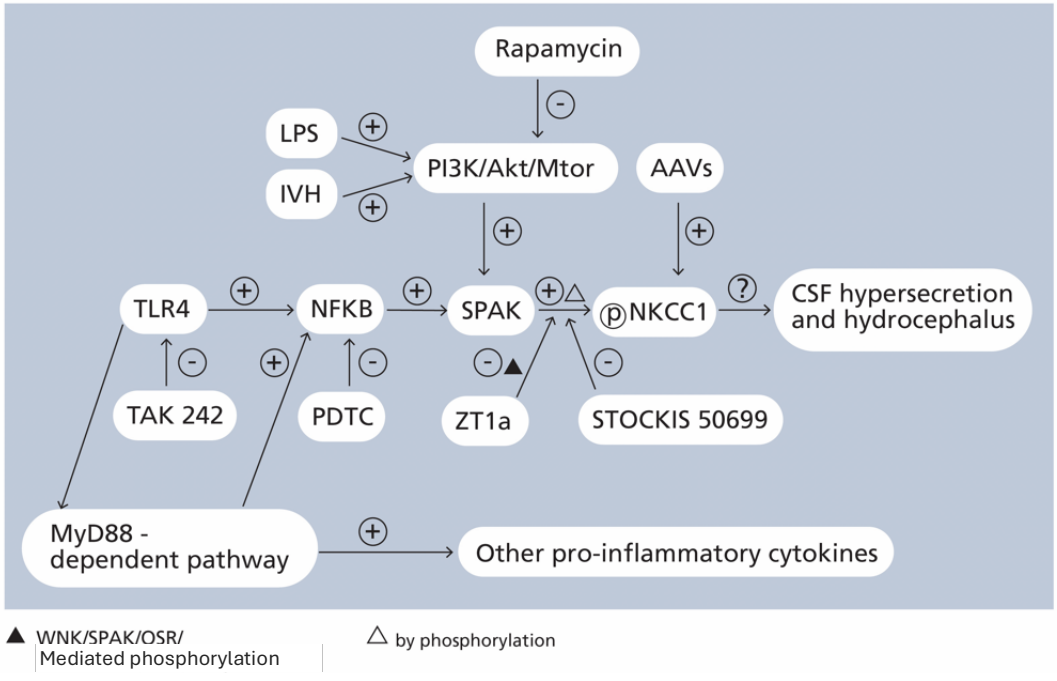

***Figure 2**: Overview of the TLR4-NKCC1 inflammatory pathway. TLR4 stimulation by inflammatory/infectious/haemorrhage related ligands leads to NFkB activation, via MyD88 dependent and non-dependent pathways. This can be inhibited with TAK 242 (TLR4) and PDTC (NFkB). This then stimulates SPAK-mediated phosphorylation of the NKCC1 channel, which increases its activity. The PI3k/Akt/Mtor pathway also feeds into this, driven by LPS and IVH. Rapamycin is an inhibitor of this pathway, whilst ZT1a and STOCKIS 50699 can inhibit the SPAK-mediated phosphorylation. Adeno-associated viruses can also affect luminal membrane NKCC1 expression. Increased NKCC1 activity/expression/phosphorylation likely drives CSF hypersecretion and hydrocephalus, but the evidence is not fully conclusive.*

The NLRP3 inflammasome

Another driver in ChP inflammation is the NLRP3 inflammasome. This has been shown to play an important role in driving neuroinflammation in intracerebral haemorrhage and BBB breakdown[91,92], and it has been investigated in a rat PHH model to assess if it has a similar effect on the ChP.

In their PHH model, Zhang et al. confirmed CSF hypersecretion, raised levels of phosphorylated NKCC1 channels and increased expression of NLRP3 components in ChP with evidence of TLR2 activation (a likely upstream mediator) and its downstream inflammatory mediators. The CSF hypersecretory response was attenuated and levels of inflammatory mediators were reduced by blocking NLRP3 with MCC950, which downregulates caspase 1 and IL-1B [69].

The downstream effects of NLRP3 upregulation led to an increase in lipid droplet formation in ChP epithelial cell mitochondria in their PHH model, with associated junctional protein disruption, such as ZO-1 and claudins[70] (figure 3). Related to this work, caspase-1 was targeted in a subarachnoid haemorrhage model of rats, where inhibition with intranasal VX765 led to improved neurological outcomes and reduced hydrocephalus[93].

Whilst these pathways are complex and partially discovered there is clear scope for continued intervention development. There is a degree of overlap with the TLR4-SPAK-NKCC1 pathways and there are several systemically administered promising therapeutic agents.

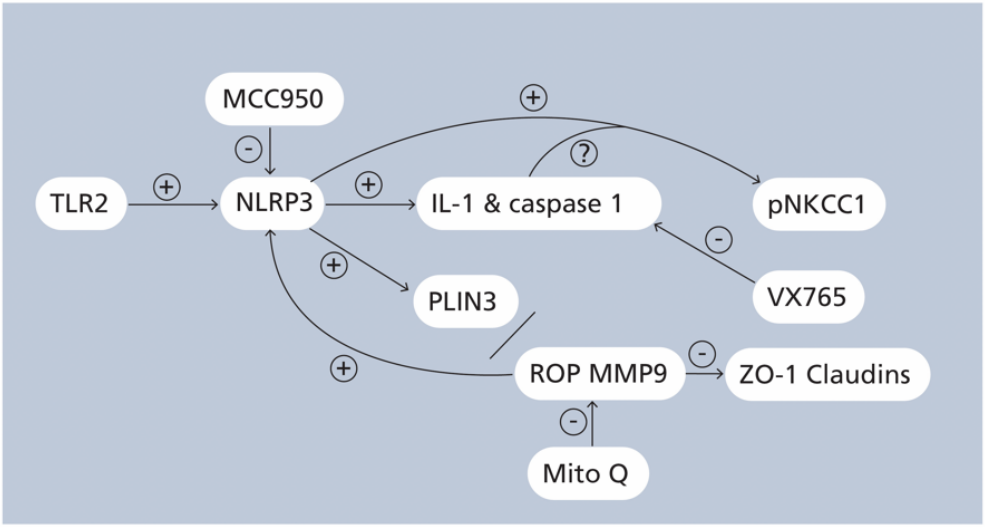

Figure 3: *Overview of the NLRP3 inflammasome pathway. TLR2 is (one of) the upstream mediators and ligand-binding results in activation of the NLRP3 inflammasome, which can be inhibited by MCC950. NLRP3 drives IL-1 and caspase-1 activity (inhibited by VX765), both inflammatory mediators. There may be a link to NKCC1 activity, which drives CSF hypersecretion. It also leads to junctional protein disruption (ZO-1, claudins) via PLIN3 (inhibited with CAY10650) , increased reactive oxygen species (ROP, inhibited with MitoQ) and matrix metallopeptidase 9 (MMP9), which will disrupt choroid plexus function. The exact interaction of these molecules is unknown, but the reactive oxygen species may drive NLRP3 activity via a positive feedback loop.*

The use of intraventricular stem cells

Another treatment option exploits the ability of stem cells to modulate inflammatory responses. The use of intraventricularly injected mesenchymal stem cells (MSCs) in a rat IVH model led to improved neurological outcomes and attenuated hydrocephalus[94]. Whilst not specifically assessing the ChP, the authors reported reduced levels of inflammatory cytokines in the CSF at 26 days post-injury. They postulate that the wider, multi-modal anti-inflammatory properties of MSCs[95,96] may make them a more capable therapeutic agent. Intraventricular administration of MSCs in a rabbit pup model of IVH [97] also alleviates hydrocephalus. This work analysed the impact on specific brain structures, including the ChP. The use of MSCs restored transforming growth factor beta (TGFβ), CTFG and MMP9 levels as well as the expression of ChP AQP1 and AQP4 in ventricular wall ependyma. There was no demonstrable impact on TLR/NFKB signalling pathways, however. Endogenous neural stem cell recruitment has also been achieved in a rodent model[98].

These experiments demonstrate potential for a more multi-faceted approach which may be less targeted but similarly effective. It will be necessary to establish which exact pathways it interferes with.

Iron and other blood-breakdown products

The earliest point of intervention in the disease process of PHH, bar preventing the initial bleed, is to address the harmful effects of the blood breakdown products, such as iron[99], with the aim to reduce its impact on the ChP and other CNS structures.

A key target is iron chelation with deferoxamine, its pathway is shown in figure 4. Rat models involving IVH, haemoglobin, or separate intraventricular iron injections[100–102] lead to hydrocephalus and the use of protoporphyrin IX, an iron-deficient haem-precursor, did not have this effect, suggesting iron is a causative agent[101]. These experiments demonstrated increased levels of WNT1/WNT3a pathway markers[100], which is linked to fibrosis in other organs[103]. The concurrent administration of deferoxamine drastically reduces the rates of hydrocephalus and lowers the iron concentrations in CSF and the WNT1/3a activity levels[100]. Importantly, delayed administration of deferoxamine is also effective[104].

Models of germinal matrix haemorrhage (GMH) or $FeCl_3$ injection demonstrated reduced levels of iron regulatory protein 2 (IRP2) and increased NCBE (figure 1, figure 4) in the ChP in conjunction with CSF hypersecretion[105]. Excess iron may be a driving factor, with IRP2 as an intermediary, as the use of iron chelation and siRNA to interfere with NCBE/NBCn2 (Slc4a10) expression attenuate these changes. Other work has demonstrated increased expression of Na/K-ATPase, NKCC1 and AQP1[102] under similar conditions. Iron metabolism within the CNS environment is a complex process in normal and abnormal physiological conditions, with significant scope for future research[106]. Once again, we see overlap with previously discussed inflammatory pathways.

Other components of blood can also trigger pro-inflammatory responses after IVH, such as peroxideroxin-2, the most abundant protein in erythrocytes after haemoglobin. When present intraventricularly, it is pro-inflammatory and induces hydrocephalus in a rat model[107]. It leads to active recruitment and migration of macrophages in the ChP. By targeting recruited macrophages with clodronate liposomes the hydrocephalic response can be attenuated[107] .

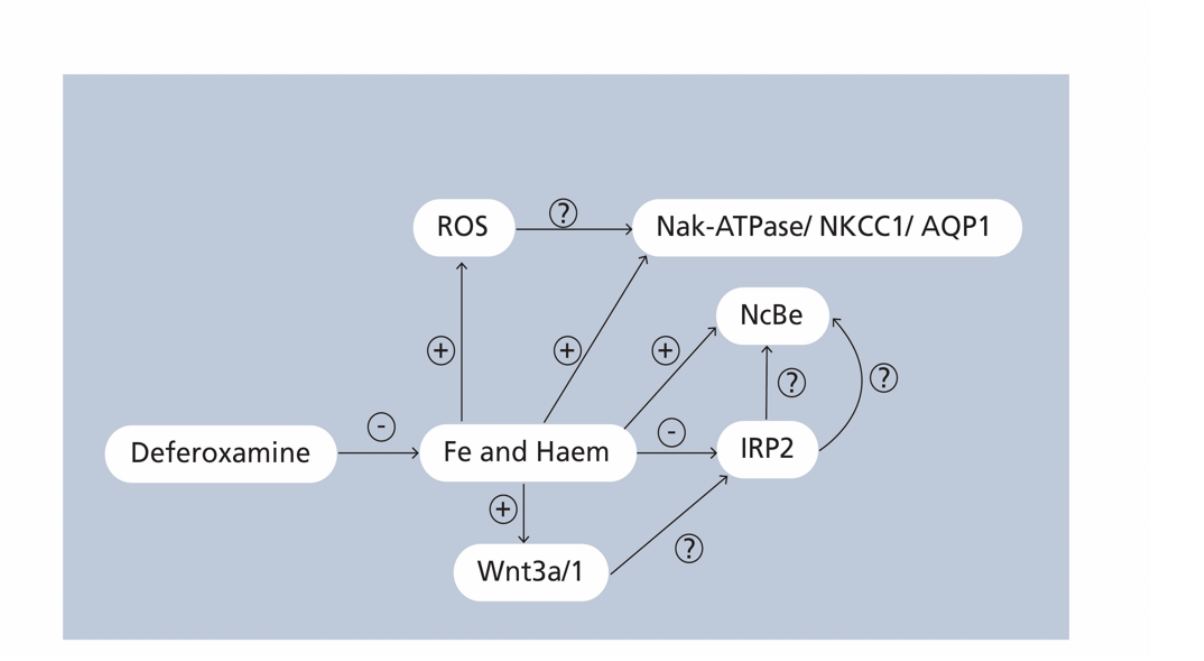

***Figure 4**: Overview of the iron/haem breakdown pathway. Deferoxamine chelates iron (Fe) and reduces the inflammatory burden of Fe and haem. These likely drive a CSF hypersecretory response through stimulation of NaK ATPase, NKCC1 and AQP1 activity in the choroid plexus, with reactive oxygen species as a possible intermediary. The pathways remain unknown, but increased levels of WNT1/3a markers were found. Iron regulatory protein 2 (IRP2) is involved, as its reduced levels are associated with increased Fe and sodium-bicarbonate cotransporter electroneutral (NCBE) activity, which is involved in CSF production. This is inhibited by iron chelation and siRNA interference. Ferroptosis, with raised levels of ROS and lipid peroxidation, has also been identified as a key marker in the ChP in the context of PHH, though whether this is cause or effect is unclear[137].*

TRPV4 and lysophosphatidic acid

Lysophosphatidic acid (LPA), which worsens neurological outcomes in haemorrhagic events[108] can induce hydrocephalus[109]. LPA may be contributing to PHH, as it is present in platelets and bound to albumin[110] and its intraventricular administration causes chronic hydrocephalus[111]. LPA receptors 1 and 3 are key in this pathway, demonstrated in knockout mice and with LPA1R inhibitor AM095[111] .

The TRPV4 channel is widely expressed in many organ tissues[112], including the ChP. It is purported to mainly be involved in calcium influx and is activated by osmotic changes, pressure changes, direct mechanical stress[113].

There appears to be a link between LPA and the TRPV4 channel in the development of PHH. The pathway is shown in figure 5. Raised levels of LPA were found in human CSF after SAH and in rat models of PHH. Intraventricular LPA replicates the development of PHH in rats and was used to investigate its downstream effectors[109]. It promotes TRPV4 activity and leads to raised intracranial pressure and CSF production. Inhibition of TRPV4 alleviates hydrocephalus and CSF

hypersecretion, whereas activation worsens this. This may be explained by the fact that TRPV4 colocalises with NKCC1.

As suggested in these studies, LPA-mediated TRPV4 activity may represent a parallel pathway in the development of PHH, possibly amplifying the inflammatory cascades described before[20,82,114] , contributing to increased NKCC1 activity. The TRPV4 pathway may represent a more immediate effect, followed by the inflammatory cascade and a delayed ciliopathy through TRPV4 agonism[109] , which could explain the findings of Lummis et al[111] and supplement pathological findings in hydrocephalus beyond the ChP.

A promising agent in this field is GSK2798745, an orally active TRPV4 channel blocker, with no significant side-effects in humans in a study assessing its pharmacokinetic profile [115], making it a suitable agent for future trials. Anti-LPA antibodies have been used in traumatic spinal cord injury mouse models and may also be a potential therapeutic agent[108].

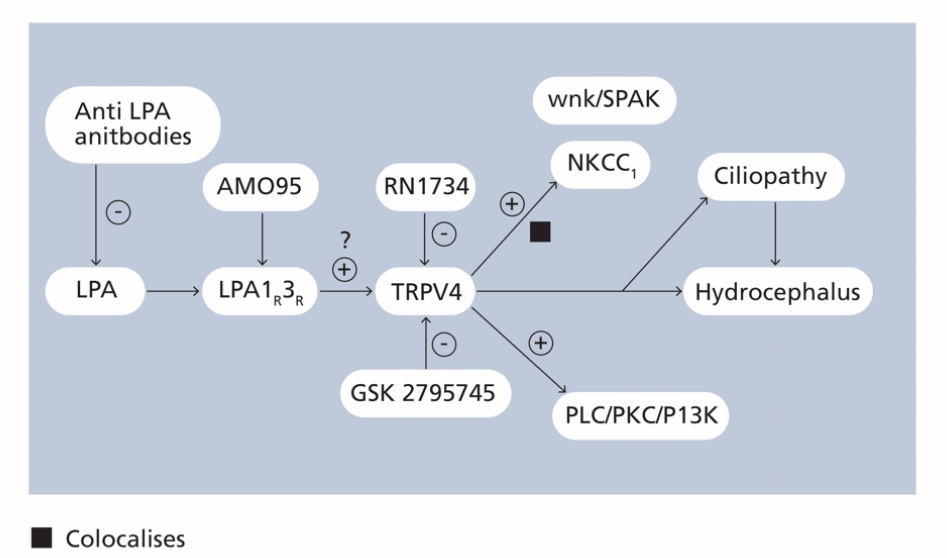

***Figure 5**: Overview of the LPA/TRPV4 pathway. TRPV4 is central in this pathway and LPA is a key activating ligand, acting via LPA1 and 3 receptors. These steps can be inhibited by anti-LPA antibodies and AMO95 respectively. TRPV4 drives CSF hypersecretion via NKCC1 activation, with which it colocalises. Wnk/SPAK mediated phosphorylation may play a role in this. PLC, PKC and PI3K are also involved in TRPV4 driven increases in trans-epithelial ion fluxes in a human ChP cell line[138]. TRPV4 activation with an agonist increases ion-flux across a porcine ChP cell line, likely by activation of calcium dependent channels[139].In a rat model of congenital hydrocephalus (one that is orthologous to Meckel-Gruber syndrome type 3), the administration of RN1734, a TRPV4 antagonist, completely prevented the ventricular dilation that otherwise develops[140]. There may be several downstream effects of TRPV4 activation, as there are also reported links to a delayed ciliopathy that can contribute to hydrocephalus.*

Other targets: TGFβ1 and aquaporin-1

Transforming growth factor Beta-1 (TGFβ1) has been of interest since it was found to be elevated in both animal and human studies of CNS injury[116–118], for example after SAH where it follows a biphasic pattern, especially in patients that develop hydrocephalus. Inhibition of the TGFβ1 pathway with decorin[119–123] , urokinase[124] and cannabinoid receptor agonists[125] have demonstrated promising results in attenuating hydrocephalus, but no clear links with CSF hypersecretion from the choroid plexus have yet been established. This is summarised in figure 6.

The role of AQP1 in CSF production by the ChP continues to be debated, as it is widely expressed throughout the CNS[26][5,32], specifically on both apical and basolateral sides of the ChP epithelium. In certain pathological states, AQP1 and AQP4 expression is increased, such as in rat models of hydrocephalus[126] and in choroid plexus papilloma, where resultant communicating hydrocephalus is related to higher AQP1 expression and lower expression is not[127].

AQP1 knockout models are difficult to interpret given the ubiquitous expression of the channel, but an siRNA-based approach showed promising results with a 19% reduction in CSF production in healthy rats. A more recent study that utilised viral choroid plexus-specific knockdown of either AQP1 or NKCC1 demonstrated AQP1's contribution to permeability, but it did not affect CSF production. Few other studies[128] have attempted to target AQP1 within the choroid plexus and none with demonstrable effect on CSF production. It remains unclear whether AQP1 is a key player, contributor or a meaningful target in the treatment of hydrocephalus.

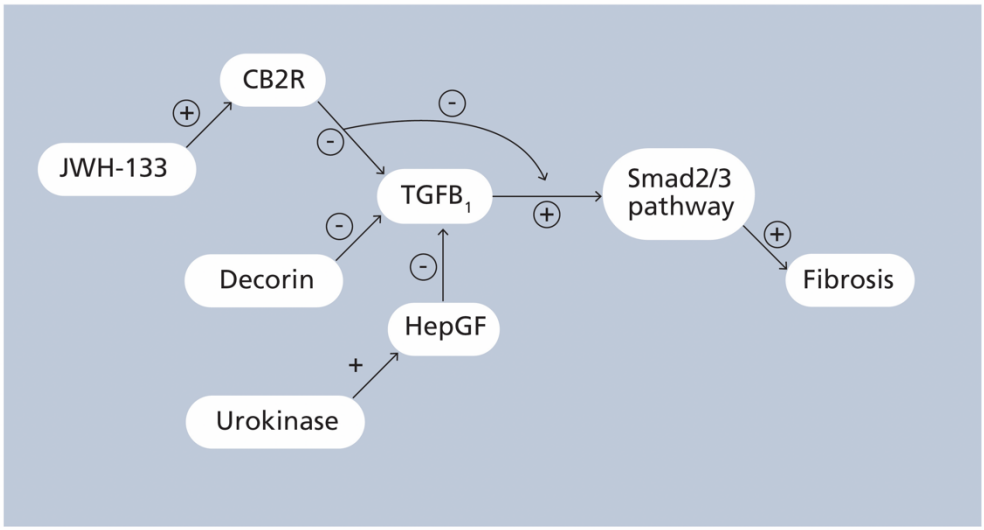

Figure 6: *Overview of the TGFB1 and fibrosis pathway. Transforming growth factor beta-1 (TGFB1) is considered key in driving post-haemorrhagic subarachnoid fibrosis, a key histological finding in patients with PHH. The Smad2/3 pathway is a downstream effector of this and decorin is a potent inhibitor of TGFB1. Urokinase has also been shown to downregulate its activity, likely via hepatocyte growth factor (HepGF). JWH-133 activates the cannabinoid-2 receptor which has as similar inhibitory effect, including on the downstream pathway.*

Barriers to translation

With such a breadth of research on therapeutic targets for hydrocephalus in rodent models, it is notable that current clinical practice does not yet reflect this. Several barriers still exist before these studies can achieve a meaningful, clinical benefit for paediatric and adult patients with hydrocephalus.

Large animal models

Besides rodent models, several studies of hydrocephalus have also been performed in higher order small animal models[129–132], but to our knowledge, none of the discussed therapeutic targets have yet been explored in large animal models of hydrocephalus, which would be the next step in translating this into clinical practice. A porcine model of hydrocephalus has been developed recently[133] , which may provide the opportunity to do so.

Other fields of translational research have been exploring molecular therapies in large animal models, such as the use of porcine models for neurofibromatosis type 1 (NF1)[134] and in the development of convection enhanced delivery for the treatment of diffuse intrinsic pontine gliomas[135].

The longevity of these animals allows more longitudinal studies and their size and physiology are more comparable to humans, allowing more accurate assessment of drug pharmacokinetics and dosing strategy, clinical outcomes and surgical intervention. There is also a reduced requirement of highly specialised miniaturised equipment as it would for smaller animals. As an example, pigs have a similar brain weight, are gyrencephalic, have a cortical and subcortical structure, and a comparable pattern of neurodevelopment to humans that makes them ideal for experimental research[136]. Presumably for these reasons, key historic experiments were carried out in large animals, by Dandy and Milhorat in dogs[33] and monkeys[41] respectively. Since these landmark experiments, experimental work has shifted focus to small animal models. The wider field of hydrocephalus research has continued to use large animal models, especially in medical device development. An overview of these studies is seen in figure 7.

Figure 7: *Overview of the major large animal model experiments in hydrocephalus.*

Canine and feline models: The cerebral windkessel mechanism was described in dogs using arterial pressure pulse, ICP, CSF withdrawal and infusions[141,142]*. The persistence of astrogliosis following ventriculoperitoneal shunt insertion was demonstrated in kittens* [143]*. CSF infusion studies with hyperosmolar solutions into the ventricular system of cats demonstrated compensatory water movement from the blood which drives up ICP without maintaining a hyperosmolar state long term* [144]*. MRI studies show that the CSF flow rate and direction can be discerned from MRI sequences in dogs using methods developed for humans* [145]*. A canine model of shunt infection is used for assessments of new shunt technologies* [146]*. Intrathecal and intravenous omeprazole reduces CSF production in dogs leading to the common treatment of the condition with the drug in veterinary practice*[147,148]*. Non-human primate models have been used to investigate antenatal surgical approaches to hydrocephalus*[149] *and the development of indwelling catheters to investigate intraventricular drug infusions*[150,151] *. In the case of non-human primates, these models offer bipedal locomotion and an arrangement of the ventricular system most comparable to humans. Ovine models: replicate human pathological observations such as corpus callosum thinning, astrogliosis and microgliosis, and develop many of the same complications after shunting*[152]*. A wireless intracranial pressure monitoring device*[153] *and a low-frequency ultrasound device designed to unblock occluded shunts*[154] *have been developed. Intraparenchymal stents were developed as an alternative to ventricular catheters and achieved resolution of kaolin-induced hydrocephalus in sheep* [155]*. Novel methods of establishing hydrocephalus have also been developed in this species using cisterna magna BioGlue injection instead of kaolin*[156]*. Porcine models: Most recently, McAllister et al published pivotal work on a pig model of kaolin-induced hydrocephalus*[133]*, demonstrating reactive astrogliosis, inflammatory cytokines in CSF and damage to the hippocampus and subgranular zone. A neonatal pig model of IVH replicated ventriculomegaly and subarachnoid fibrosis* [157,158] *and allowed the use of ultrasound imaging, shunt placement, and assessment of longitudinal changes in ICP and CSF outflow resistance. Porcine models have been used to test innovations such as in-line flow sensors within shunts that may offer early warning of failure*[159]*, ICP sensors*[160–163] *and new designs for endoscopic equipment*[164]*.*

The importance of such models in the development of novel treatments for hydrocephalus cannot be overstated. As research practices moved to less neurodevelopmentally sentient models, the continued relevance of these models remains clear from the available data and methodological approaches achievable in these species, with large animal progression a crucial next step in this field of translational hydrocephalus research. Important factors that complicate this progression are summarised in figure 8 and these need to be addressed to advance the field.

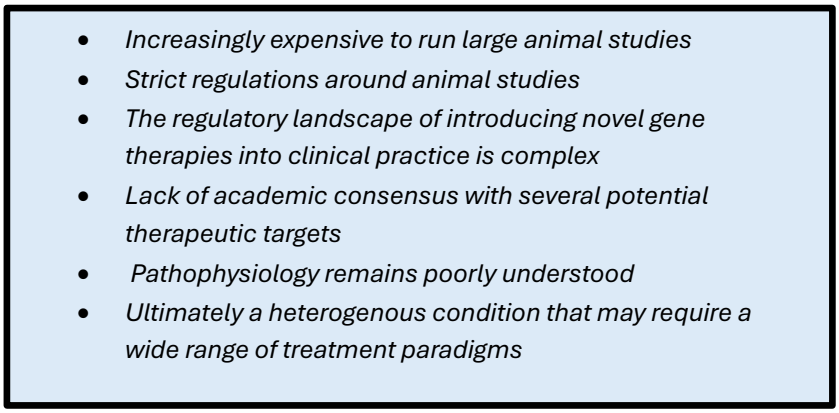

***Figure 8**: Important barriers to translational research targeting the choroid plexus*

Conclusion

The evidence-base to use these novel approaches to target choroid plexus function is highly promising. In addition to a resurgence of surgical methods, there is now a wide array of molecular agents that may act as therapeutic targets. Consistent positive results achieved in small animal models provide ample of scope for future research.

Given the complex interplay of molecular pathways and concurrent pathophysiological processes, future research should investigate the use of combination therapies in treating hydrocephalus. Inhibiting multiple pathways in the same model may produce a synergistic or additive effect which may be pathophysiology dependent. Similarly, an intraventricular route of administration may help reduce systemic and local side-effects of therapeutic agents and improve its end-organ efficacy. This may also allow combined surgical and targeted pharmacological treatment.

Knowing the clinical, social and economic burden of hydrocephalus and our current approach to its treatment, we should acknowledge the importance of advancement of this research. Despite promising results and significant conceptual advances, no targeted agents have yet been trialled in large animal models. It is encouraging that large animal models for hydrocephalus are being developed[133], as they will play a key role in translating such therapies into clinical practice, for both surgical and pharmacological options. Focusing research aims to translation will ultimately lead to better clinical outcomes for our patients.

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Abbreviations

AE2	anion exchanger 2
Akt	Protein kinase B
AQP	aquaporin
BBB	Blood brain barrier
BCSFB	Blood CSF barrier
ChP	Choroid plexus
ChPE	choroid plexus epithelium
CHPECs	choroid plexus epithelial cells
CSF	cerebrospinal fluid
CTFG	connecting tissue growth factor
DRIFT	drainage, irrigation and fibrinolytic therapy
ECM	extracellular matrix
ETV	endoscopic third ventriculostomy
EVD	external ventricular drain
GABA	gamma-aminobutyric acid
ICP	intracranial pressure
ICV	intracerebroventricular
IL-1B	interleukin-1 beta
IVH	intraventricular haemorrhage
KCC	potassium chloride cotransporter
LPA	lypophosphatidic acid
MMP9	matrix metallopeptidase 9
mTOR	mechanistic target of rapamycin
myD88	myeloid differentiation primary response 88

N-KA	sodium-potassium ATPase
NBCe2	sodium-bicarbonate cotransporter electrogenic 2
NCBE	sodium bicarbonate cotransporter electroneutral
NF1	neurofibromatosis type 1
NFKB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
NKCC1	sodium-potassium co-transporter 1
NLRP3	Nucleotide-binding Oligomerization Domain, Leucine Rich Repeat and Pyrin Domain Containing 3
OSR1	Odd-Skipped Related Transcription Factor 1
PHH	Post-haemorrhagic hydrocephalus
PI3K	phosphoinositide 3-kinase
PKC	protein kinase C
PLC	phospholipase C
PLIN3	perilipin 3
siRNA	small interfering RNA
SPAK	STE20/SPS1-related Proline-Alanine-rich Kinase
TGFb	transforming growth factor beta
TLR2	Toll-like receptor 2
TLR4	toll-like receptor 4
TRPV4	transient receptor potential vanilloid 4
WNK	with no lysine kinase
ZO-1	zona-occludens 1

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