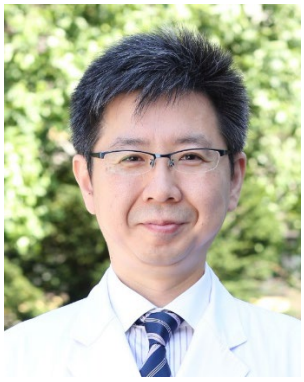
True Water Tracer for Dynamics in the Brain



Kohsuke Kudo
Hokkaido University
Faculty of Medicine Internal Medicine Department of Radiology
Professor
Kita 14-jo Nishi 5-chome, Kita-ku, Sapporo-shi, Hokkaidou
Tel: +81(11)-706-7779/5977 (PHS 83646)
Fax: +81(11)-706-7876
e-mail: kkudo@huhp.hokudai.ac.jp

New developments in cerebrospinal circulation research -focusing on diagnostic imaging-

In recent years, it has been discovered that there is a protein called AQP4 (aquaporin-4) that actively allows water molecules to pass through the brain. It has become clear that AQP4 is mainly involved in the hemodynamics of cerebrospinal fluid.[i] In 2012, Nedergaard et al. proposed the glymphatic theory. Glympathic theory has been reported as a new approach to the study of neurodegenerative diseases such as Alzheimer's disease.[ii] The cerebrospinal fluid that covers the brain parenchyma has been thought to play a protective role in brain tissue, but it is now known to be actively involved in brain function and disease.

In 2020, Taoka et al. summarized MRI imaging methods and cerebrospinal fluid research in a review of neuroimaging in the Glympathtic.[iii] Although the use of contrast media is effective for quantitative dynamic studies of cerebrospinal fluid, it is difficult to observe the dynamics of cerebrospinal fluid in Blood, CSF, and ISF using a single method. In the review, Water-^{17}O reports that ISF circulation within the blood-brain barrier is observed.[iv]

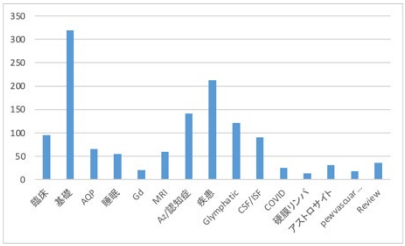
We searched for research from 2011 to the present using keywords (MRI, CSF, Glymphatic, Contrast agent, kinetics et al.,) using our database and Pubmed. This search yielded 934 researchers and 200 papers, indicating that attention is being focused on this field. Below please find additional information on the number of researchers and papers that are associated with our keywords:

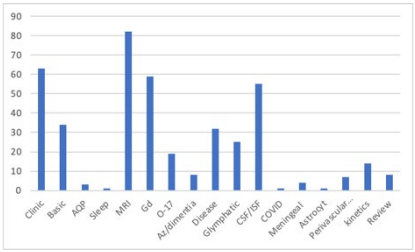
List of researchers using our database

臨床	基礎	AQP	睡眠	Gd	MRI	Az/認知症	疾患	Glymphatic	CSF/ISF	COVID	硬膜リンパ	アストロサイト	pewvascuar Virchow-Robin	Review
95	319	66	55	21	60	141	213	121	91	25	14	31	18	36

List of papers using Pubmed

Clinic	Basic	AQP	Sleep	MRI	Gd	O-17	Az/dimentia	Disease	Glymphatic	CSF/ISF	COVID	Meningeal	Astrocyt	Perivascular Virchow-Robin	kinetics	Review
63	34	3	1	82	59	19	8	32	25	55	1	4	1	7	14	8





Our database
Pubmed database

In the database, Gd preparations and Water-^{17}O were conducting clinical studies of Glymphatic using MRI contrast agents. However, subarachnoid endoscopy of Gd contrast showed adverse events of severe headache (28%) and severe nausea (34%). Kudo et al. investigated the intracerebral distribution and initial dynamics of cerebrospinal fluid by intravenous administration of Water-

^{17}O saline to humans and confirmed the safety, and it suggests the usefulness of MRI on cerebrospinal fluid dynamics.[v]

Igarashi et al. examined water flux to the cortex, basal ganglia, and third ventricle in AQP-1 and AQP-4 knockout mice using Water-^{17}O, and demonstrated that water influx into the CSF is regulated by AQP-4, not AQP-1.[vi] Huber et al. found that TGN-073, an AQP-4 accelerator, increased interstitial fluid turnover and greatly reduced Water-^{17}O content in the cerebral cortex, despite normal flux to the cerebrospinal fluid.[iv] Zhang et al. showed a significant decrease in peak and steady-state Water-^{17}O uptake into the brain in adult AQP-4KO mice, even though CBF was unchanged.

The concept of the glymphatic system has been proposed as a mechanism for waste removal in the brain. So far, PET of water-150 has been used to visualize the water itself. However, water-150 PET has a short half-life (approx. 2 min), making it impossible to analyze the dynamics of water. Water-^{17}O can be a promising tool for long-term water dynamics analysis with high resolution. AQP, a water channel in the cell membrane, is said to be involved in the pathogenesis of Alzheimer's, and Water-^{17}O can be applied to the analysis of aquaporin function.

Cerebral spinal cord circulation research is showing new developments, and many new findings on cerebral circulation are being obtained, and new possibilities for diagnosis and treatment of intractable diseases such as Alzheimer's are emerging.

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[i] Taoka T, J Mag Reson Imging 2020; 4; 11

[ii] Iliff JJ, Wang M, Lioa Y, et al., Sci Transl Med 2012; 4; 147ra111

[iii] Taoka T, Naganawa S, Korean J Radiol 2020; 21; 11; 1199

[iv] Huber VJ, Igarashi H, Ueki S et al., Neuroreport 2018; 29; 697

[v] Kudo K, Harada T, Kameda H et al., Magn Reson Med Sci 2018; 17; 223-230

[vi] Zhang Y, Xu K, et.al., PLoS ONE 14(6): e0218415

Contact information

① TAIYO NIPPON SANSO Corporation.

Fuji Bldg. 5-30-9 Shiba, Minato-ku, Tokyo 108-0014, Japan
Tel: +81(3)5439-5897
Fax: +81(3)5439-5883
e-mail: Isotope.TNS@tn-sanso.co.jp

② Matheson Tri-Gas
Tel: (510)410-5316
e-mail: dzunzanyika@mathesongas.com