糖尿病と酸化ストレス

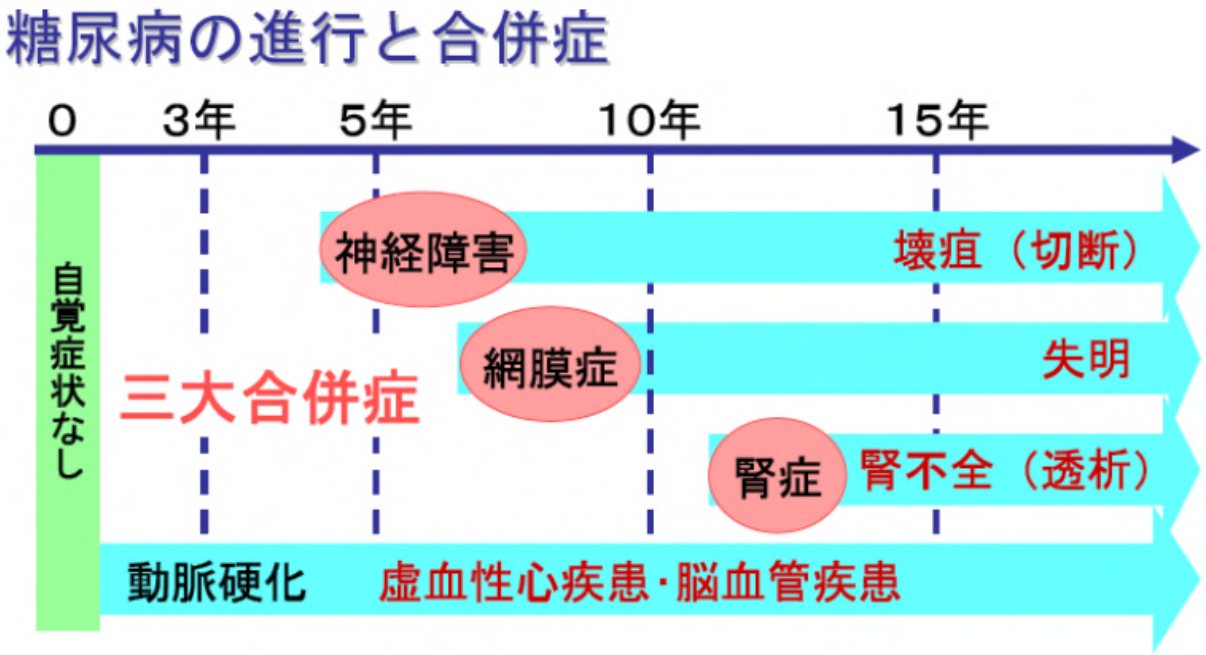
-ペリサイトをターゲットとした治療戦略-

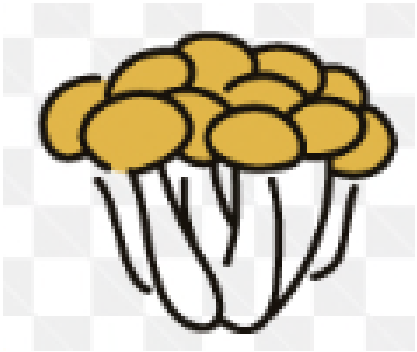
Review

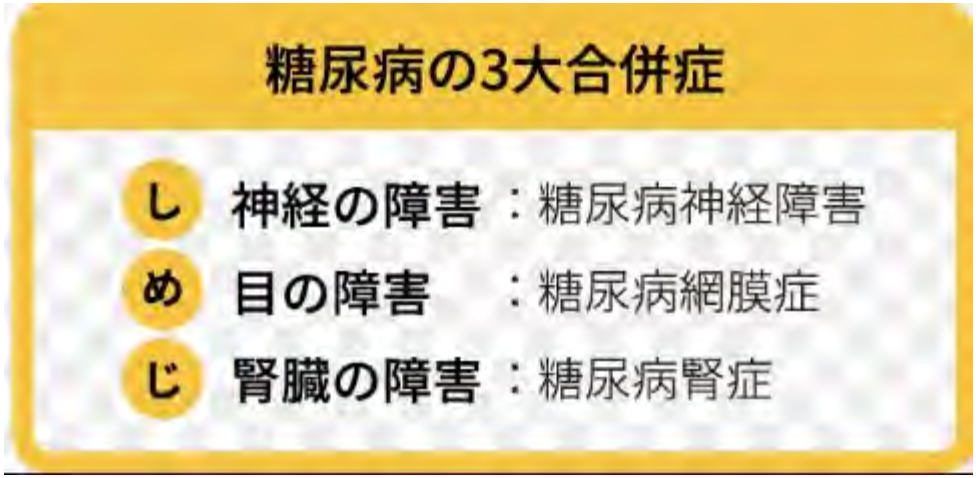
May 14, 2019

諸藤　陽一

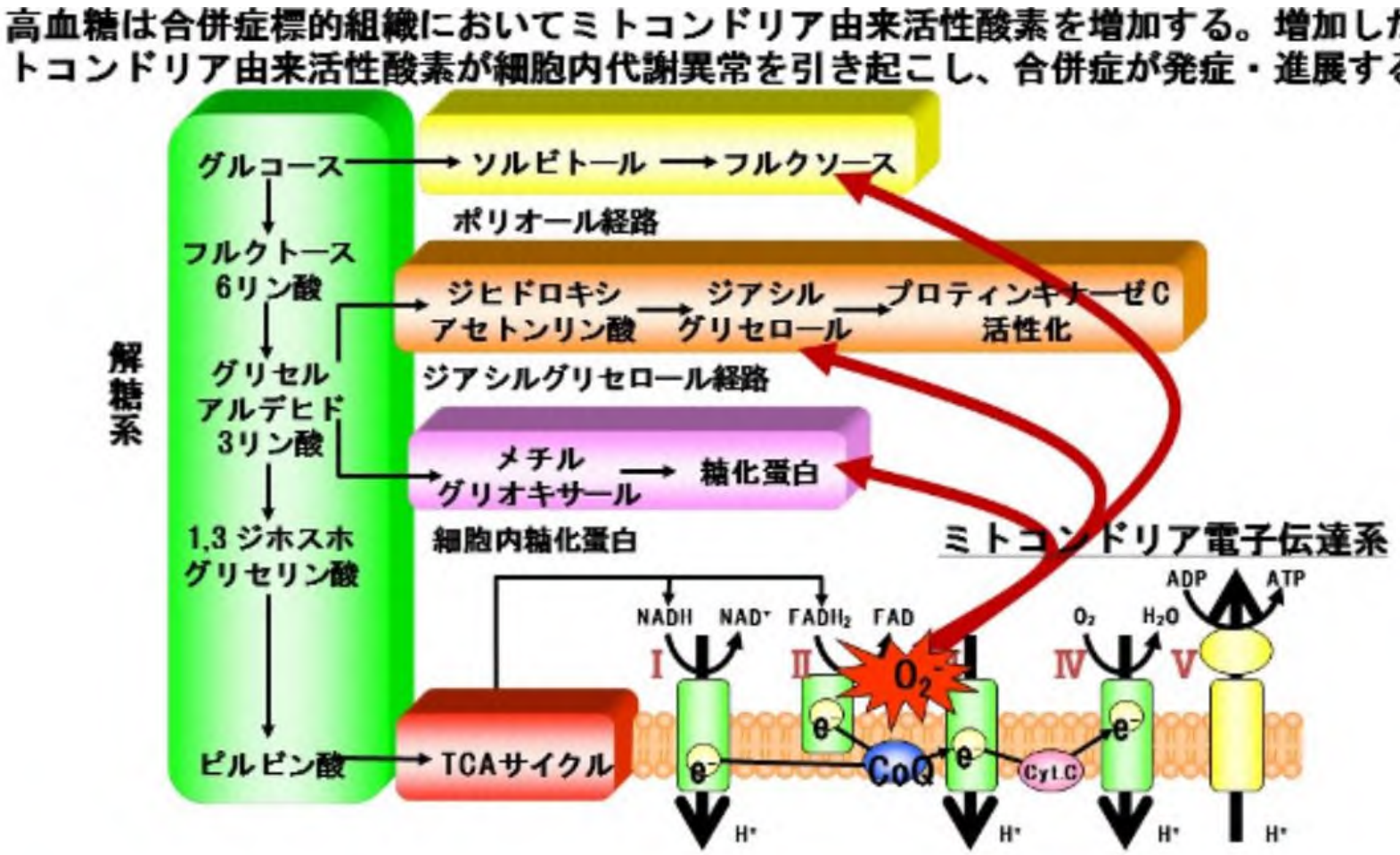
糖尿病の合併症


糖尿病の進行と合併症
0
3年
5年
10年
15年
自覚症状なし
三大合併症
神経障害
壊疽（切断）
網膜症
失明
腎症
腎不全（透析）
動脈硬化
虚血性心疾患・脳血管疾患




糖尿病の3大合併症
し 神経の障害 ：糖尿病神経障害
め 目の障害 ：糖尿病網膜症
じ 腎臓の障害 ：糖尿病腎症

高血糖による組織障害の機序



Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, Kaneda Y, Yorek MA, Beebe D, Oates PJ, Hammes HP, Giardino I, Brownlee M. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature. 2000;404(6779):787-90

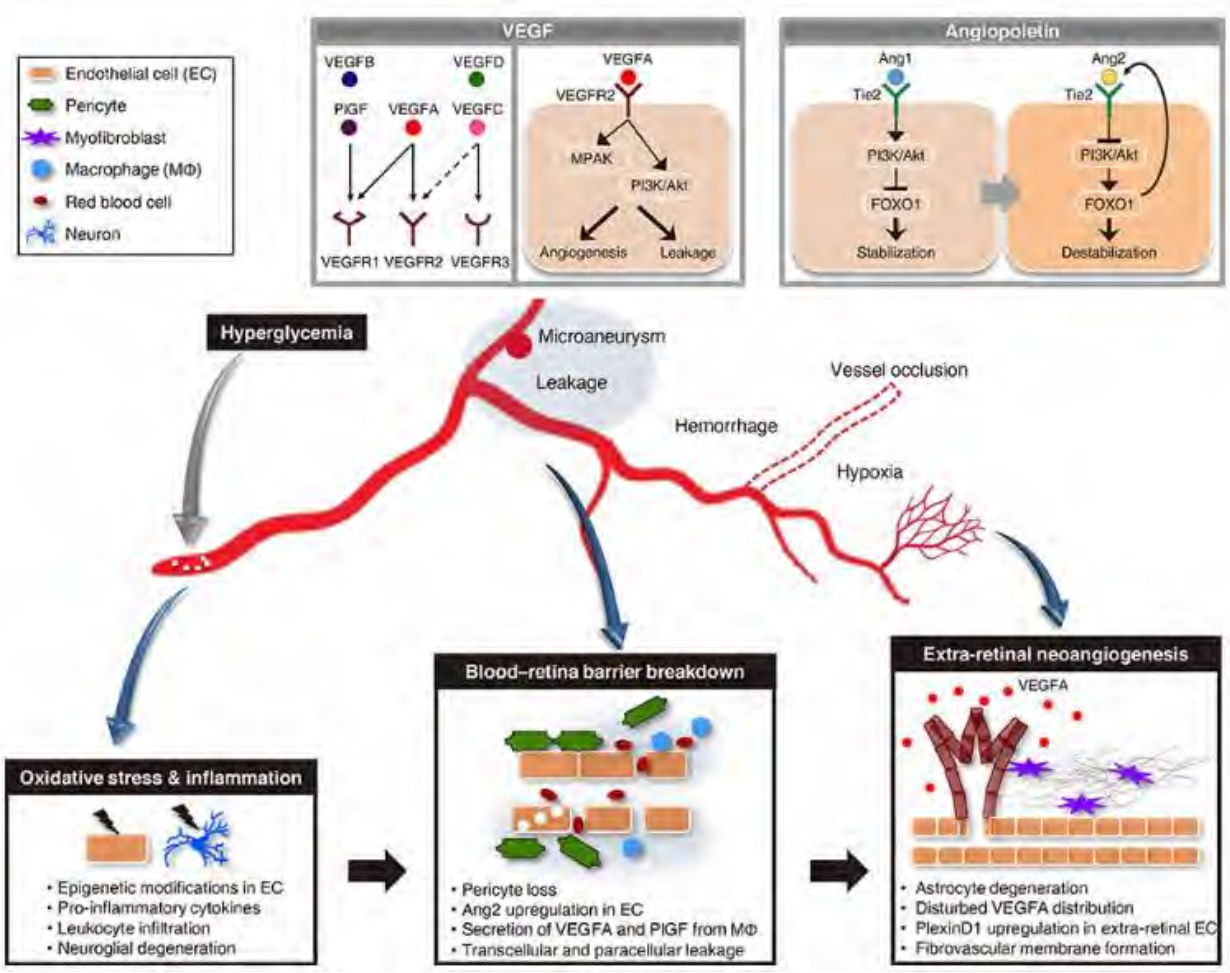
http://www.nho-kumamoto.jp/medical/kumamotouniversity/kumamotouniversity-complications.html

糖尿病における微小血管障害： 脳では？

- ✓ Diabetes eventually results in changes in the microvasculature of the brain and retina, leading to retinopathy and dysfunction and disruption of the blood–brain barrier (BBB) (Banks et al., 1997; Huber et al., 2006).
- ✓ Diabetes is also associated with cognitive dysfunction and an increased risk of Alzheimer's disease (Ott et al., 1999) that is associated with the microvascular and neurovascular unit (NVU) changes (Hayden et al., 2013).

糖尿病における微小血管障害：ペリサイトの関与

糖尿病性網膜症



Kusuhara S et al., Diabetes Metab J. 2018

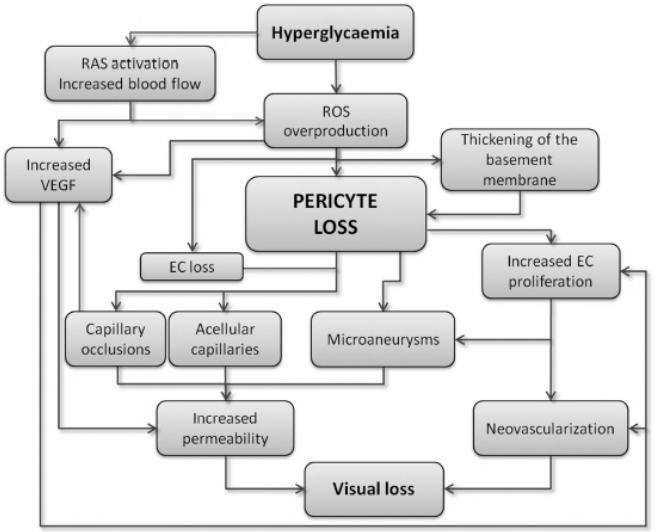
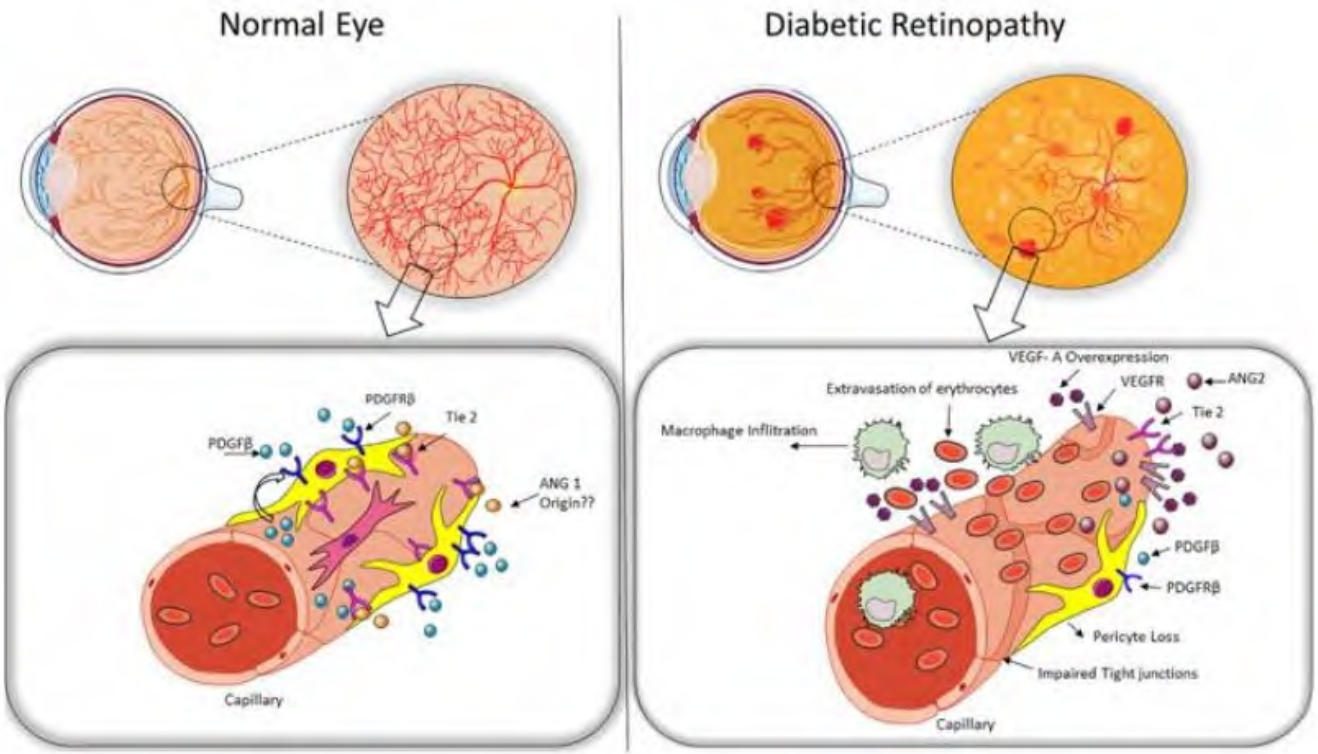


Fig. 1. *Mechanisms and consequences of pericyte loss in the pathogenesis of diabetic retinopathy.*

Beltramo E et al., 2013



Retinal vasculature in diabetic retinopathy. Pericytes are present around blood vessels in the normal retina. Pericyte dropout is one of the major hallmarks of diabetic retinopathy. Park and colleagues now suggest that pericytes are essential in the formation and maturation of blood-retinal-barrier at the postnatal stage through active recruitment of pericytes onto the growing retinal vessels.[3] Nevertheless, pericytes are not indispensable in the adult stable retinal blood vessels; and their selective depletion did not lead to a phenotype similar to diabetic retinopathy. Future studies may reveal other role of retinal pericytes in much greater detail.

Santos G et al., Eye, 2018

糖尿病性網膜症はペリサイトロスの代表的疾患

糖尿病における微小血管障害：ペリサイトの関与

糖尿病性末梢神経障害

Diabetologia. 2011 Jun;54(6):1517-26. doi: 10.1007/s00125-011-2107-7. Epub 2011 Mar 16.

Advanced glycation end-products induce basement membrane hypertrophy in endoneurial microvessels and disrupt the blood-nerve barrier by stimulating the release of TGF-β and vascular endothelial growth factor (VEGF) by pericytes.

Shimizu F[1], Sano Y, Haruki H, Kanda T.

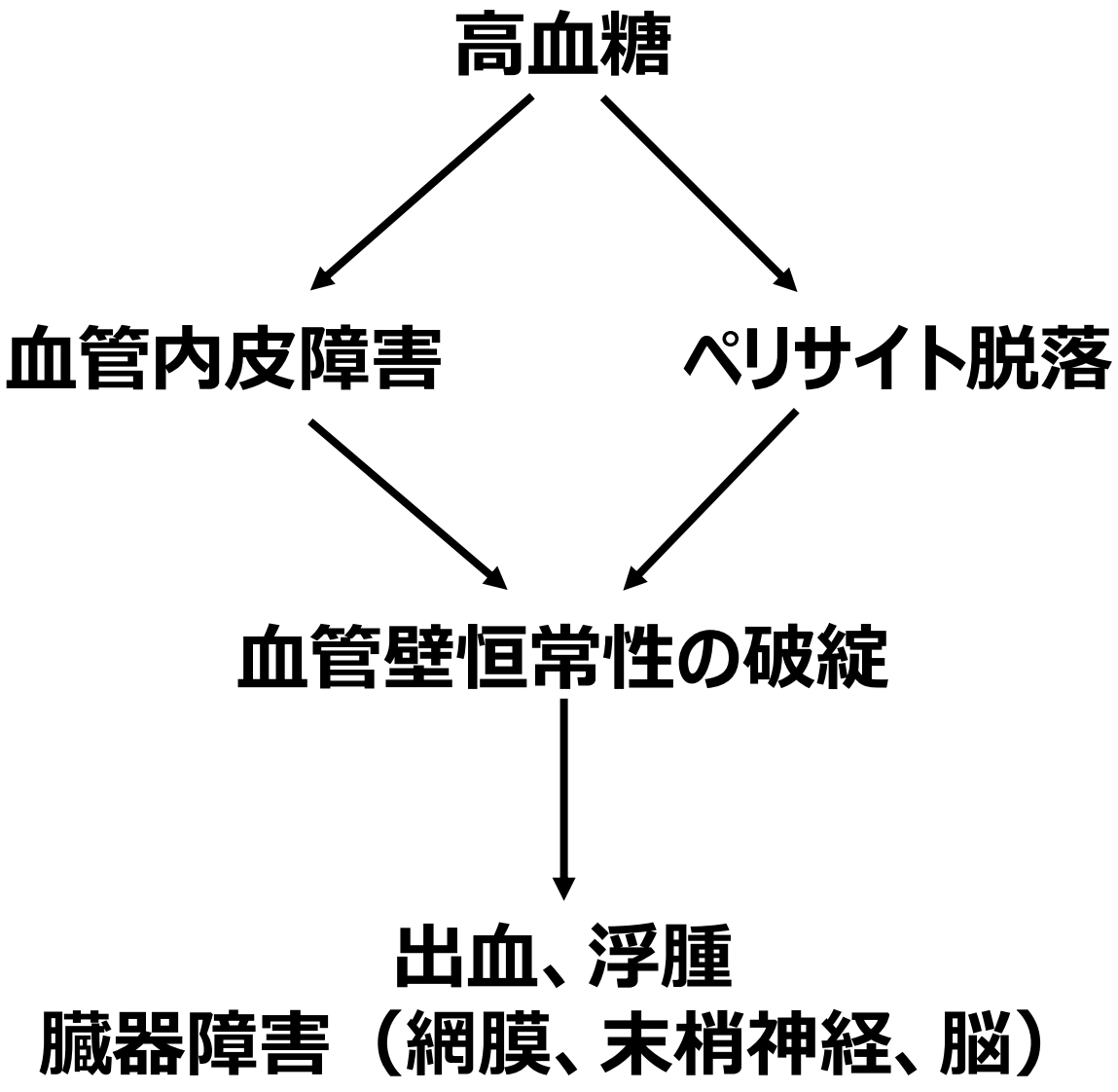
Abstract

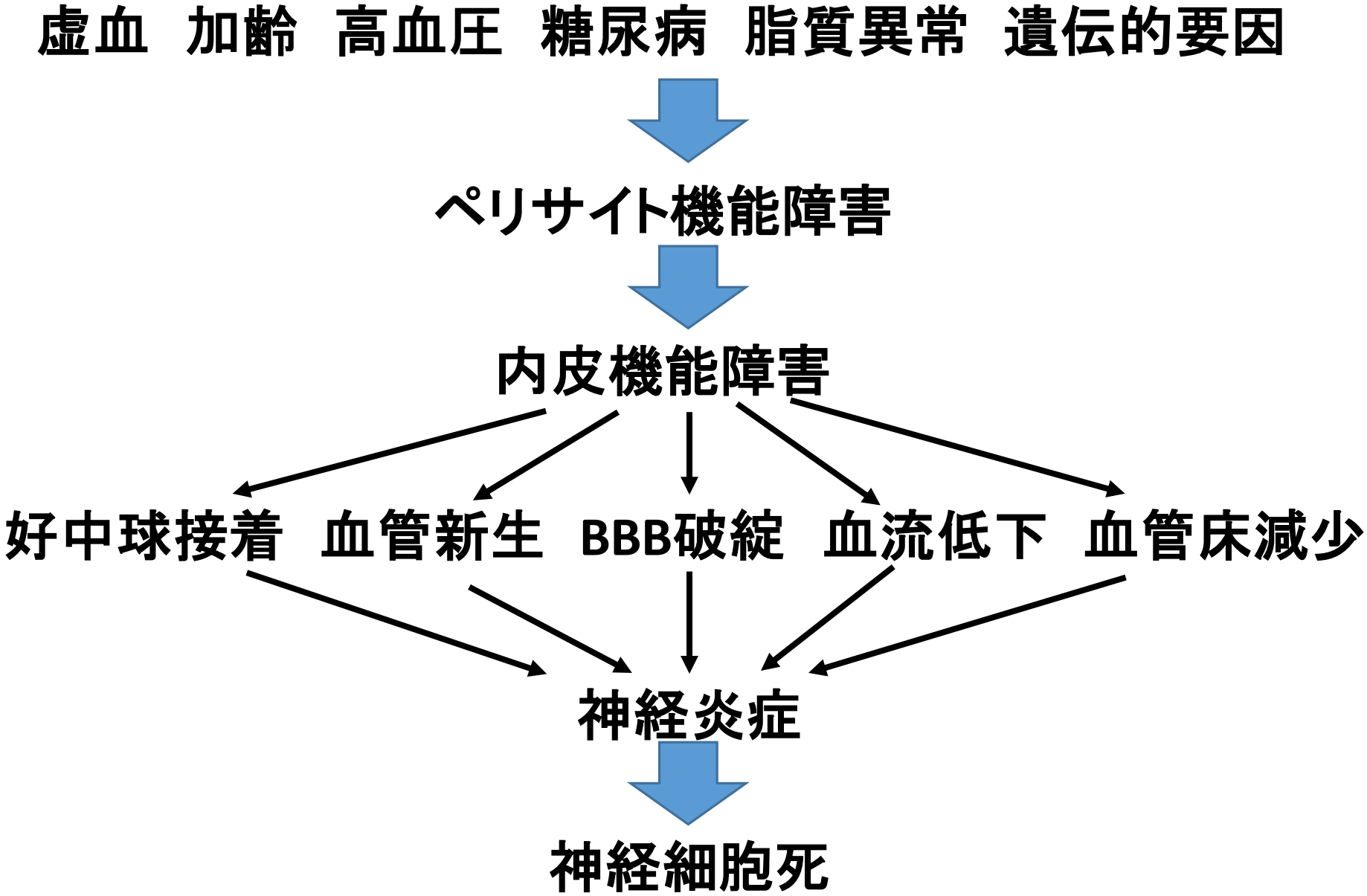
AIMS/HYPOTHESIS: The breakdown of the blood-nerve barrier (BNB) is considered to be a key step in diabetic neuropathy. Although basement membrane hypertrophy and breakdown of the BNB are characteristic features of diabetic neuropathy, the underlying pathogenesis remains unclear. The purpose of the present study was to identify the possible mechanisms responsible for inducing the hypertrophy of basement membrane and the disruption of the BNB after exposure to AGEs.

METHODS: The newly established human peripheral nerve microvascular endothelial cell (PnMEC) and pericyte cell lines were used to elucidate which cell types constituting the BNB regulate the basement membrane and to investigate the effect of AGEs on the basement membrane of the BNB using western blot analysis.

RESULTS: Fibronectin, collagen type IV and tissue inhibitor of metalloproteinase (TIMP-1) protein were produced mainly by peripheral nerve pericytes, indicating that the basement membrane of the BNB is regulated mainly by these cells. AGEs reduced the production of claudin-5 in PnMECs by increasing autocrine signalling through vascular endothelial growth factor (VEGF) secreted by the PnMECs themselves. Furthermore, AGEs increased the amount of fibronectin, collagen type IV and TIMP-1 in pericytes through a similar upregulation of autocrine VEGF and transforming growth factor (TGF)-β released by pericytes.

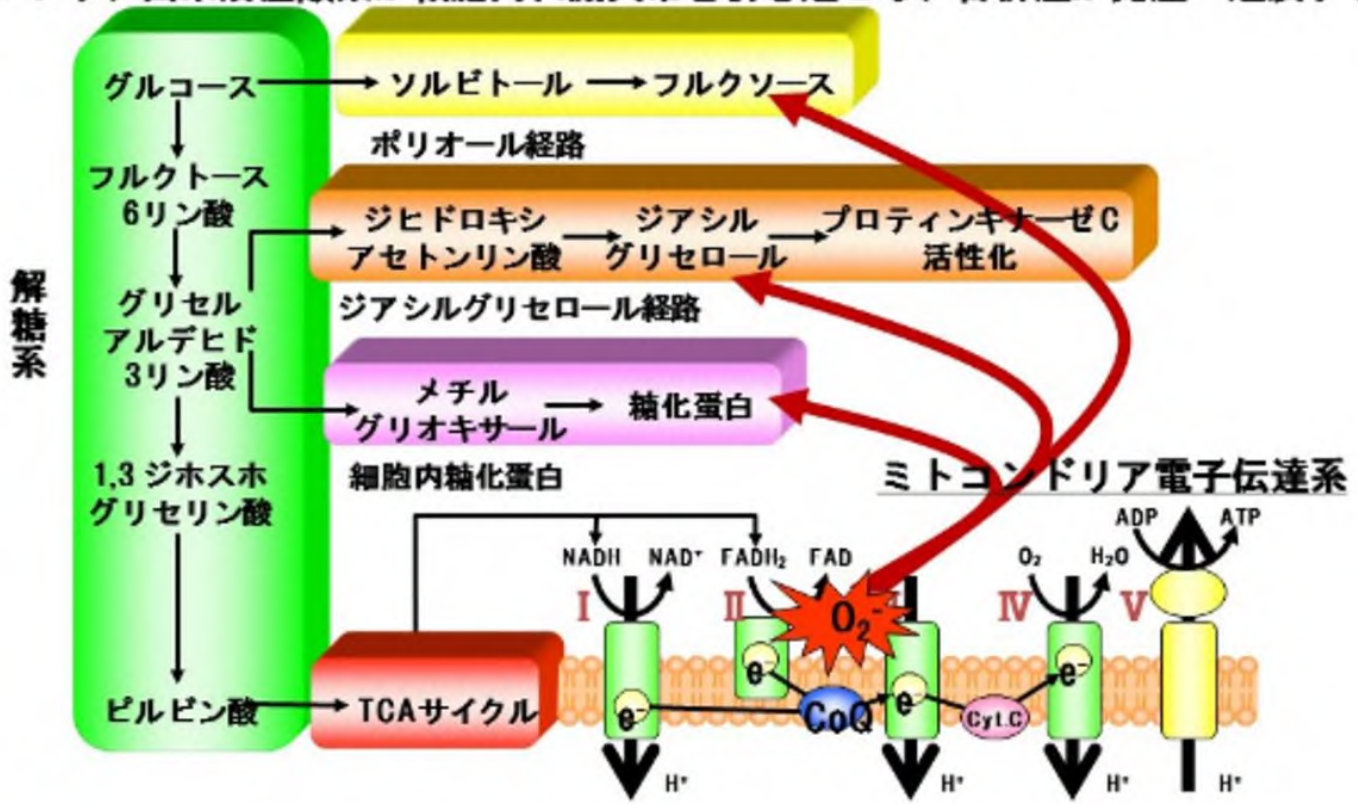
CONCLUSIONS/INTERPRETATION: These results indicate that pericytes may be the main regulators of the basement membrane at the BNB. AGEs induce basement membrane hypertrophy and disrupt the BNB by increasing autocrine VEGF and TGF-β signalling by pericytes under diabetic conditions.


高血糖
血管内皮障害
ペリサイト脱落
血管壁恒常性の破綻
出血、浮腫
臓器障害（網膜、末梢神経、脳）


虚血　加齢　高血圧　糖尿病　脂質異常　遺伝的要因
ペリサイト機能障害
内皮機能障害
好中球接着
血管新生
BBB破綻
血流低下
血管床減少
神経炎症
神経細胞死

糖尿病合併症に対する治療選択のひとつとして

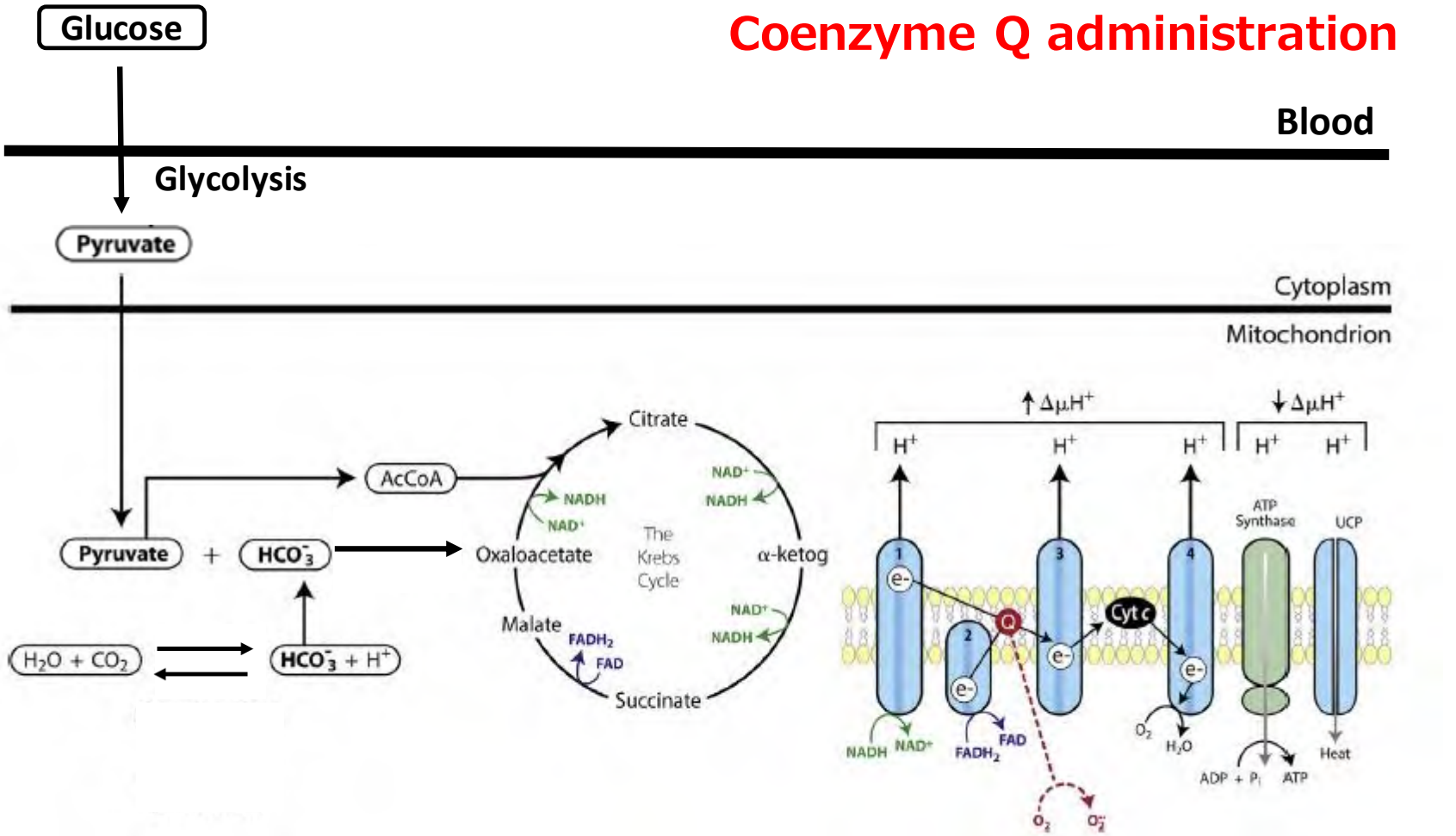
高血糖は合併症標的組織においてミトコンドリア由来活性酸素を増加する。増加したミトコンドリア由来活性酸素が細胞内代謝異常を引き起こし、合併症が発症・進展する。



superoxideの産生を抑える

Decreasing superoxide formation is a viable therapeutic option to combat hyperglycemia induced tissue damage, especially in the brain, which is the most metabolically active tissue in the body.

superoxideの産生を抑える

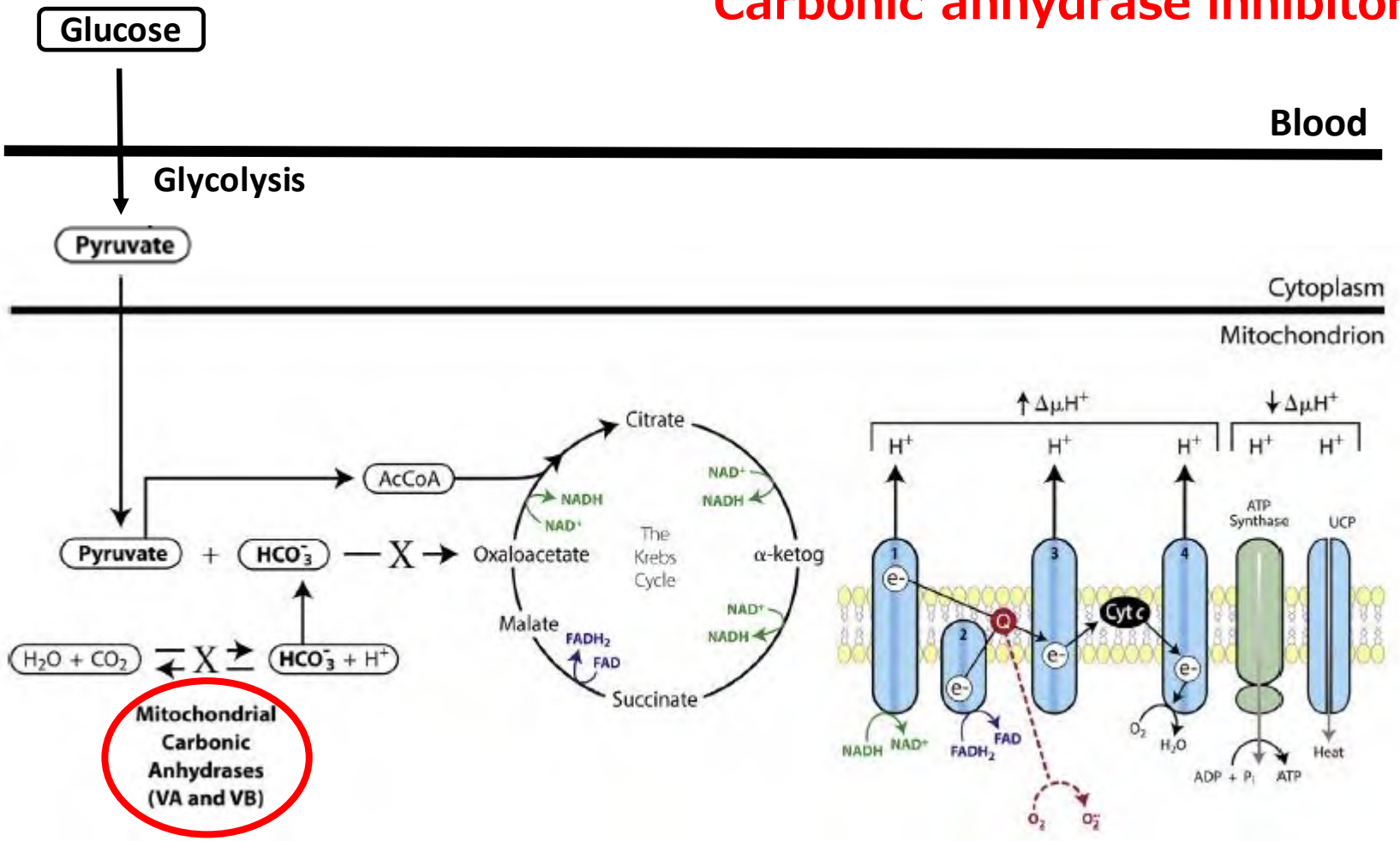


Shah GN, Morofuji Y,. Biochem Biophys Res Commun. 2013

Increased hyperglycemia-derived electron donors from the Krebs generate a high mitochondrial membrane potential by pumping protons across the mitochondrial inner membrane. Coenzyme reduces O2 to superoxide. Low coenzyme Q levels have been correlated with a number of neurodegenerative diseases, cancer, diabetes, and vascular disease.

superoxideの産生を抑える

Carbonic anhydrase inhibitor



We hypothesize that similar to EC, cerebral pericyte suffer higher oxidative stress in the hyperglycemia of diabetes. We proposed to reduce the oxidative stress by limiting the production of superoxide with the inhibition of carbonicanhydrases (CA) found in the mitochondria.

高血糖がペリサイト、BBBに与える影響

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Saint Louis University School of Medicine

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Yoichi Morofuji
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Topiramate Treatment Protects Blood-Brain Barrier Pericytes from Hyperglycemia-Induced Oxidative Damage in Diabetic Mice

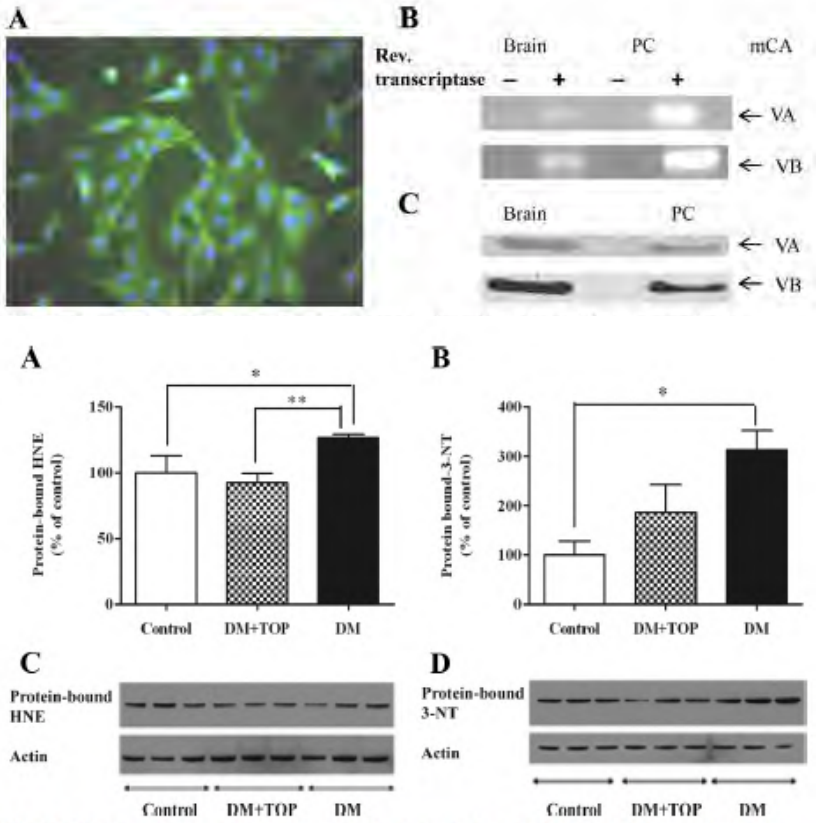


FIG. 4. Effect of topiramate treatment on diabetes-induced lipid peroxidation and protein oxidation in the mouse brain. Two days after induction of diabetes, mice (n = 10/group) were given daily sc injections of topiramate for 3 wk, and brains were analyzed for HNE and 3-NT by immunoblot analysis. The significantly high levels of HNE (A) and 3-NT (B) in the diabetic (DM) mice were reversed in topiramate-treated (DM + TOP) mice. C and D, Representative immunoblots of protein-bound HNE and 3-NT, respectively. The values are expressed as mean ± SEM (*, $P < 0.05$; **, $P < 0.01$).

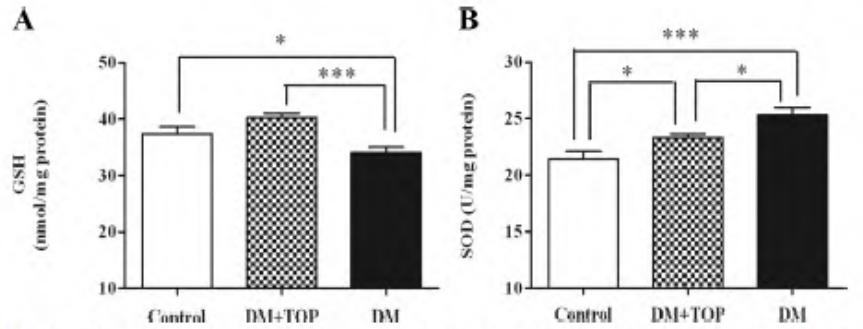


FIG. 3. Effect of topiramate treatment on diabetes-induced alterations in GSH levels and SOD activity in the mouse brain. Two days after induction of diabetes, mice (n = 10/group) were given daily sc injections of topiramate for 3 wk, and brains were analyzed for oxidative stress. GSH levels were determined by HPLC and SOD activity by measuring the inhibition of cytochrome c reduction using the xanthine/xanthine oxidase $O_2\bullet-$ generating system. A, The significantly lower GSH levels in the diabetic animals (DM) were restored to control levels by topiramate treatment (DM + TOP). B, The SOD activity was significantly lower in the mice treated with topiramate compared with untreated diabetic mice. The values are expressed as mean ± SEM (*, $P < 0.05$; ***, $P < 0.001$).

Price TO et al.,Endocrinology, 2012

Topiramate Treatment Protects Blood-Brain Barrier Pericytes from Hyperglycemia-Induced Oxidative Damage in Diabetic Mice

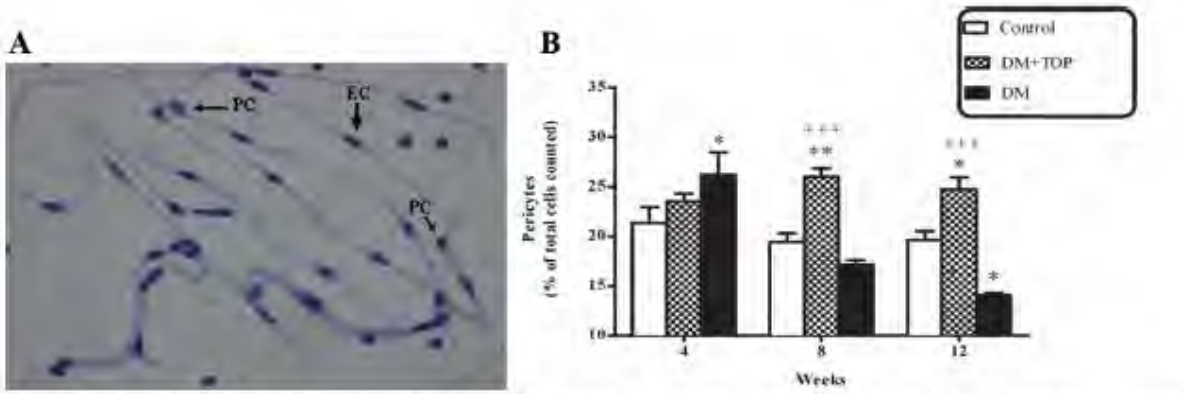
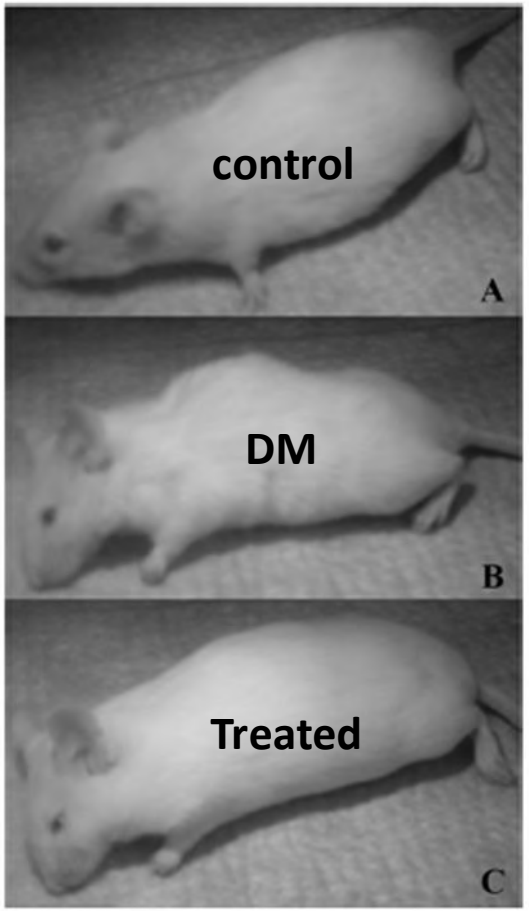


FIG. 6. Topiramate treatment rescued diabetes-induced PC loss in the cerebral microvasculature. Diabetic mice (n = 10) were treated with d injections of topiramate for up to 12 wk. Brains were harvested at 4, 8, and 12 wk of topiramate treatment, cerebral microvessels were isola and stained with PAS-hematoxylin on chamber slides. A, Captured PAS-hematoxylin-stained microscope image of isolated mouse brain microvessels. *Thinner arrows* point to prominent round nuclei of PC, and *thick arrows* points to elongated cigar-shaped nucleus of EC. The P EC, in the isolated microvessels, were counted, and percent of PC/total cells was calculated. B, Percent of PC at 4, 8, and 12 wk of topiramat treatment. After an initial significant increase in PC numbers in diabetic mice at 4 wk of diabetes, the numbers declined below normal at 8 w became significantly less at 12 wk. The PC numbers remain high in topiramate-treated mice at 8 and 12 wk of diabetes. Values are mean ± [*, $P < 0.05$; **, $P < 0.01$ compared with control; +++, $P < 0.001$ comparison between treatments (DM *vs.* DM+TOP)]. DM, Diabetic mic + TOP, diabetic mice treated with topiramate.



These results provide the first evidence that inhibition of mitochondrial CA activity reduces diabetes-induced oxidative stress in the mouse brain and rescues cerebral PC dropout. Thus, mitochondrial CA may provide a new therapeutic target for oxidative stress related illnesses of the central nervous system.

Price TO et al.,Endocrinology, 2012

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http://dx.doi.org/10.1124/jpet.112.201400
J Pharmacol Exp Ther 344:637–645, March 2013

Pharmacological Inhibition of Mitochondrial Carbonic Anhydrases Protects Mouse Cerebral Pericytes from High Glucose-Induced Oxidative Stress and Apoptosis[S]

Gul N. Shah, Tulin O. Price, William A. Banks, Yoichi Morofuji, Andrej Kovac, Nuran Ercal, Christine M. Sorenson, Eui S. Shin, and Nader Sheibani

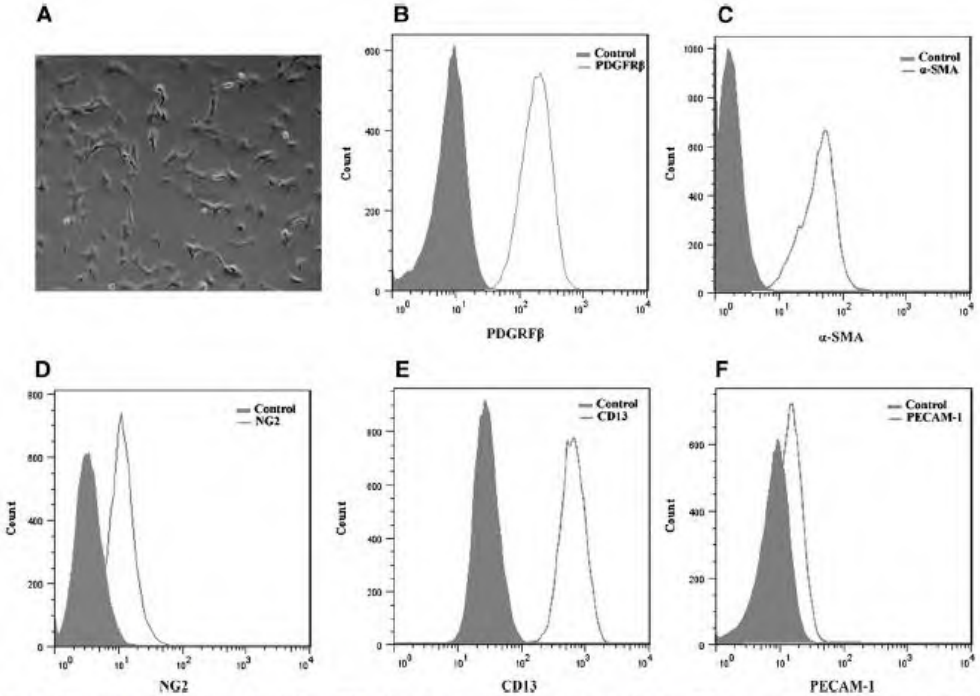

Fig. 1. Characterization of IPCs. (A) Morphology of IPCs cultured on uncoated plates (10x magnification). IPCs were stained for PDGFR-β (B), α-SMA (C), NG2 (D), and CD13 (E), all of which were expressed in IPCs. (F) PECAM-1, an EC marker, is not detected in IPCs. Histogram data are presented as cell numbers versus log fluorescence intensity of individual cell markers. The controls, shaded histograms, were either cells without antibody (B and F) or treated with a secondary antibody (C–E) only. These experiments were performed three times with similar results.

TABLE 1

Effect of LPS on the release of cytokines and chemokines by IPCs

IPCs were exposed to LPS (1 μg/ml) for 24 hours. Values are mean ± S.E.M. $n = 5$.

Cytokine/Chemokine	Control	Treated
	pg/ml	*pg/ml*
IL-1α	0.26 ± 0.05	0.42 ± 0.03*
IL-1β	N.D.	5.54 ± 0.56
IL-4	0.55 ± 0.06	1.42 ± 0.02**
IL-5	1.66 ± 0.09	2.58 ± 0.11**
IL-6	2.34 ± 0.49	522.55 ± 50.06**
IL-12 (p40)	N.D.	0.73 ± 0.29
IL-12 (p70)	N.D.	5.24 ± 0.70
IL-13	N.D.	20.08 ± 2.30
IL-17	1.47 ± 0.07	2.44 ± 0.14**
GM-CSF	1.12 ± 0.06	22.65 ± 1.64**
KC	306.56 ± 22.91	37,631.75 ± 16,842.57
MCP-1	3544.39 ± 209.10	11,930.87 ± 386.03**
MIP-1α	1.38 ± 0.14	15.50 ± 1.32**
MIP-1β	N.D.	3.04 ± 0.25
RANTES	147.46 ± 13.88	844.01 ± 122.29**
TNF-α	N.D.	5.85 ± 0.09

GM-CSF, granulocyte macrophage colony-stimulating factor; IL, interleukin; IPC, conditionally immortalized cerebral pericyte; KC, keratinocyte-derived chemokine; LPS, lipopolysaccharide; MCP-1, monocyte chemo-attractant protein-1; MIP, macrophage inflammatory protein; N.D., not detected; RANTES, regulated on activation normal T cell expressed and secreted; TNF-α, tumor necrosis factor.

*$P < 0.05$; **$P < 0.01$ for difference from controls.

Conditionally immortalized cerebral pericyte (IPC) cultures were established from Immortomice to investigate the effect of high glucose on oxidative stress and pericyte apoptosis.

Shah GN et al., J Pharmacol Exp Ther, 2013

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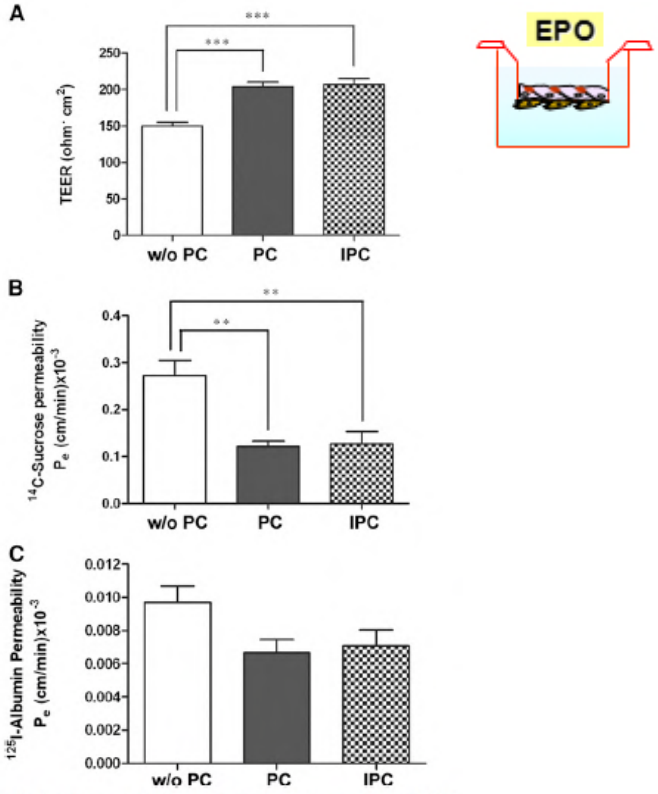

Fig. 2. Comparison of TEER and transendothelial permeability of BBB models. The triple models constructed with IPCs imposed the same TEER (A) and transendothelial permeability (B and C) as the ones constructed with PCs compared with the double models without PCs. The TEER (expressed as $\Omega \times cm^2$) was higher (A) and transendothelial permeability coefficient (P_e) [expressed as (cm/min) $\times 10^{-3}$] was lower for paracellular markers, ^{14}C-sucrose (B) and ^{125}I-albumin (C), in the presence of either PCs or IPCs. All data are presented as mean ± S.E.M. ($n = 4$). $^{**}P < 0.01$; $^{***}P < 0.001$.

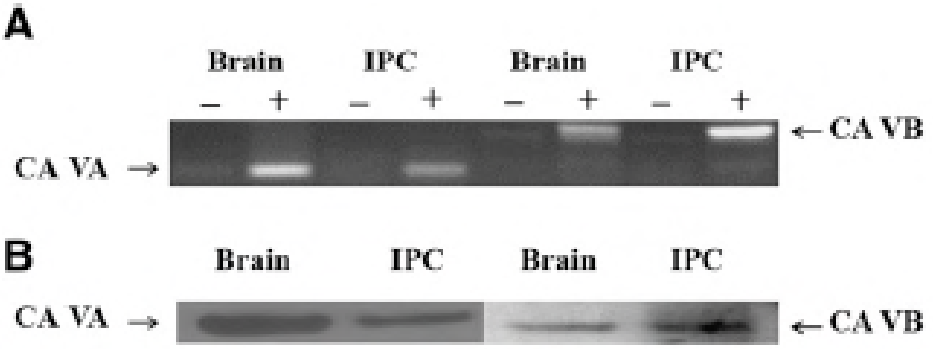

Fig. 3. Mitochondrial CA VA and VB in IPCs. (A) Transcripts of CA VA and CA VB in IPCs and the brain. Plus and minus signs indicate with and without reverse transcriptase, respectively. (B) Polypeptides of CA VA and CA VB in IPCs and the brain.

Shah GN et al., J Pharmacol Exp Ther, 2013

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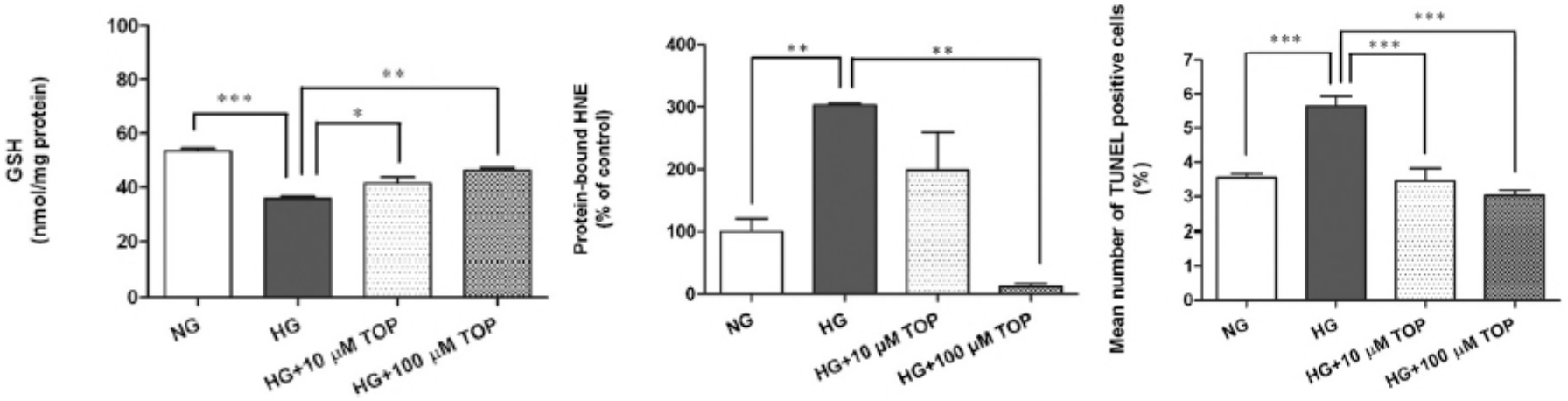

These results provide the first evidence that pharmacological inhibition of mitochondrial carbonic anhydrases attenuates pericyte apoptosis caused by high glucose-induced oxidative stress. Carbonic anhydrase inhibitors have a long history of safe clinical use and can be immediately evaluated for this new indication in translational research.

Shah GN et al., J Pharmacol Exp Ther, 2013

High glucose-induced mitochondrial respiration and reactive oxygen species in mouse cerebral pericytes is reversed by pharmacological inhibition of mitochondrial carbonic anhydrases: Implications for cerebral microvascular disease in diabetes

Gul N. Shah [a,*], Yoichi Morofuji [b,c], William A. Banks [b,c], Tulin O. Price [a]

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[b] VAPSHCS/GRECC S-182, Building 1, Room 810A, 1660 S. Columbian Way, Seattle, WA 98108, USA
[c] Division of Gerontology and Geriatric Medicine, Department of Medicine, University of Washington, Seattle, WA, USA

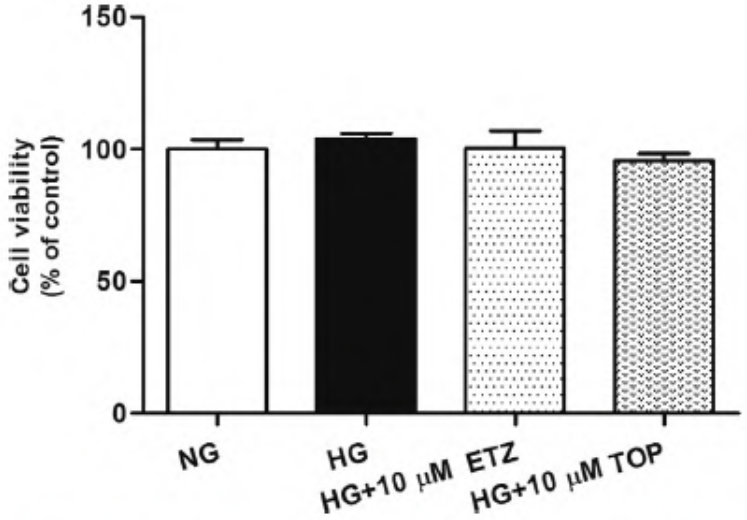


Fig. 3. Cerebral pericyte viability in NG, HG (40.7 mM), and HG with ethoxyzolamide or topiramate. Cell viability is shown as percentage of viable cells in NG. Data are shown as mean ± SEM ($n = 3$). The graphs are representative of three independent experiments. ETZ, ethoxyzolamide; HG, high glucose; NG, normal glucose; TOP, topiramate.

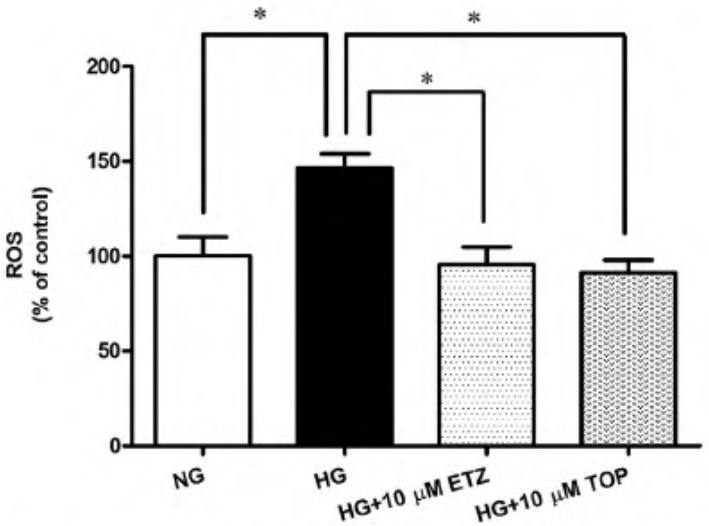
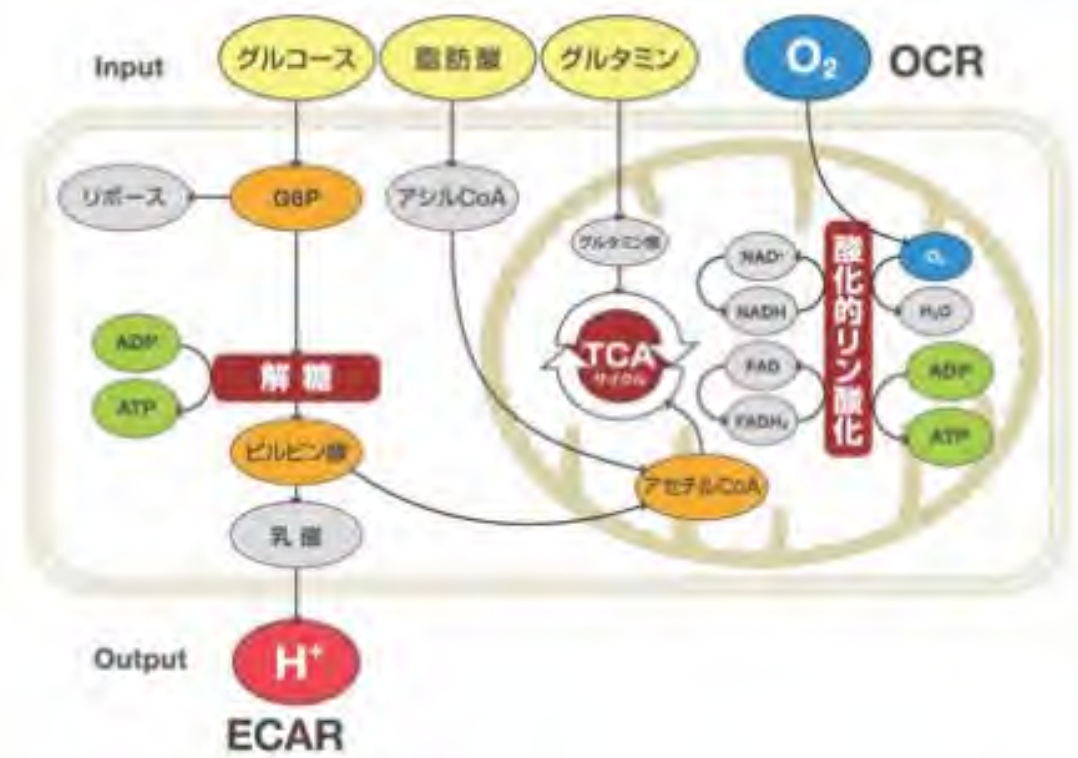


Fig. 2. Effect of mitochondrial carbonic anhydrase inhibition on high glucose-induced reactive oxygen species in cerebral pericytes. Results are presented as percentage of cells treated with NG. Data are shown as mean ± SEM ($n = 3$). The graphs are representative of three independent experiments. *$p < 0.05$. ETZ, ethoxyzolamide; HG, high glucose; NG, normal glucose; TOP, topiramate.

Shah GN, Morofuji Y, et al., Biochem Biophys Res Commun. 2013

細胞外フラックスアナライザー



細胞の主要なエネルギー代謝経路である解糖、ミトコンドリアによる好気呼吸の状態を、細胞に対して無侵襲・高感度に経時的計測が可能

- **細胞の2 つのエネルギー代謝:**
  ミトコンドリア呼吸≒酸素消費速度(OCR) ・解糖系≒細胞外酸性化速度(ECAR)の同時計測が可能
  培養細胞や単離ミトコンドリアの酸素濃度(pmol/min)・水素イオン濃度(mpH/min)の変化を、ルミネッセンス法により検知し、OCR・ECAR を算出します。

High glucose-induced mitochondrial respiration and reactive oxygen species in mouse cerebral pericytes is reversed by pharmacological inhibition of mitochondrial carbonic anhydrases: Implications for cerebral microvascular disease in diabetes

Gul N. Shah [a,*], Yoichi Morofuji [b,c], William A. Banks [b,c], Tulin O. Price [a]

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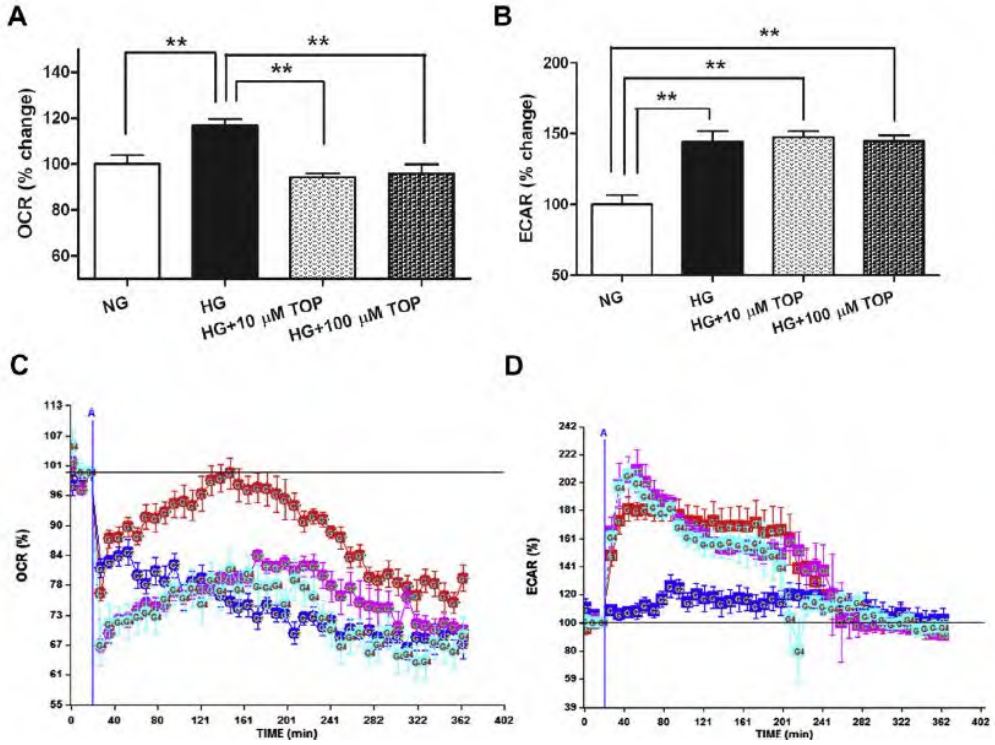
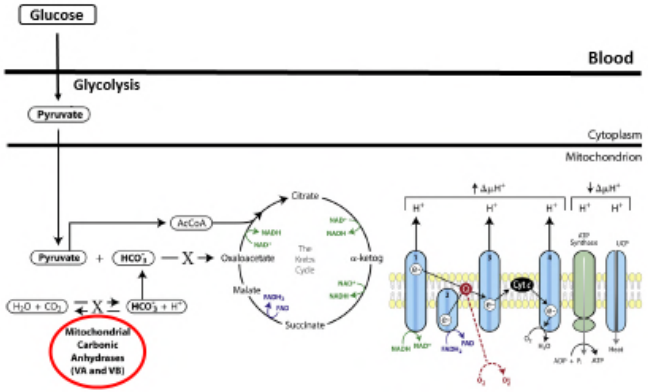
[c] Division of Gerontology and Geriatric Medicine, Department of Medicine, University of Washington, Seattle, WA, USA





These data provide new evidence that pharmacological inhibitors of mitochondrial carbonic anhydrases, already in clinical use, may prove beneficial in protecting the brain from oxidative stress caused by ROS produced as a consequence of hyperglycemia-induced enhanced respiration.

Shah GN, Morofuji Y, et al., Biochem Biophys Res Commun. 2013

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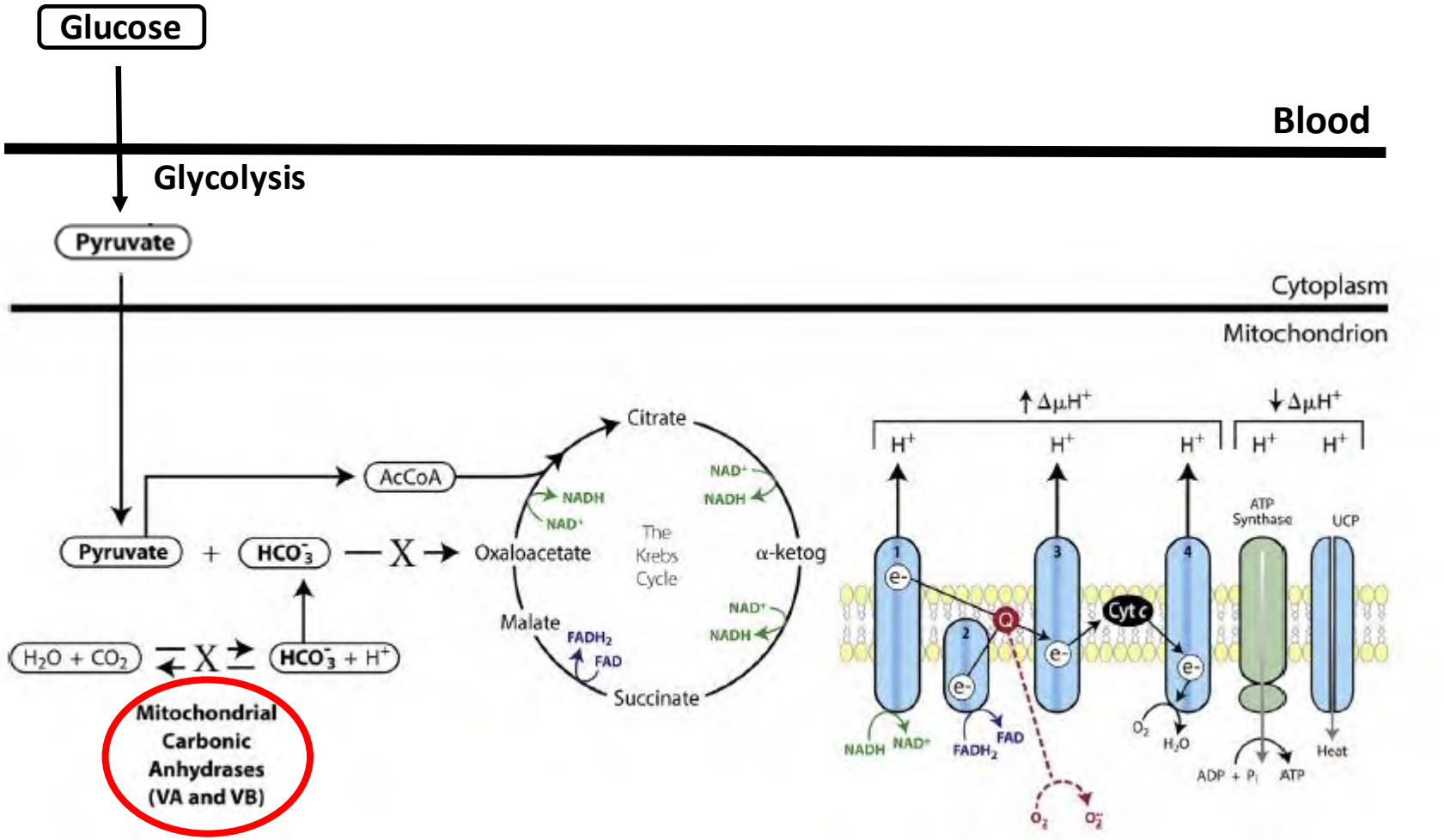


Shah GN, Morofuji Y, et al., Biochem Biophys Res Commun. 2013

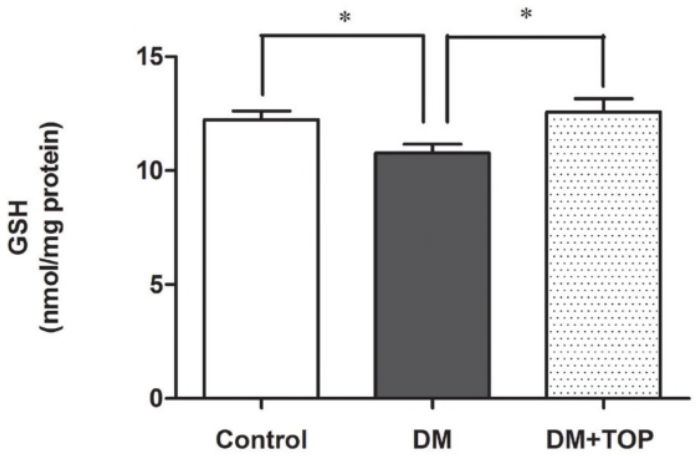
Int Libr Diabetes Metab. 2015 March ; 1(1): 6–12.

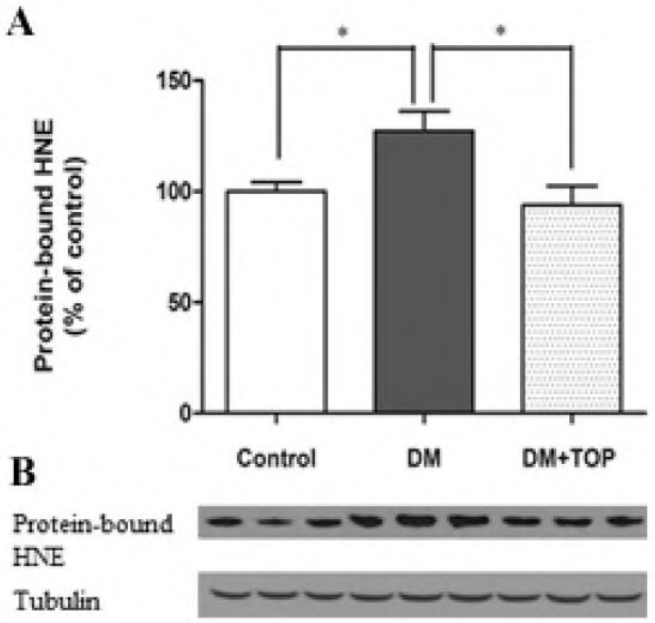
Protective Effect of Topiramate on Hyperglycemia-Induced Cerebral Oxidative Stress, Pericyte Loss and Learning Behavior in Diabetic Mice

Tulin O. Price[1], Susan A. Farr[2,3], Michael L. Niehoff[3], Nuran Ercal[4], John E. Morley[1,3], and Gul N. Shah[1,✉]

[1]Division of Endocrinology, Department of Internal Medicine, Saint Louis University School of Medicine, St. Louis, MO, USA

Previously, we reported that topiramate, a mitochondrial CA inhibitor, at a dose of 50 mg/kg/day protects the brain in diabetes by reducing oxidative stress and restoring pericyte numbers. In an effort to reduce the toxicity associated with higher doses of topiramate, the current study was designed to investigate the effect of 1.0 mg/kg topiramate on reducing oxidative stress, restoring pericyte numbers in the brain, and improving the impaired learning behavior in diabetic mouse.





Price TO et al., Int Libr Diabetes Metab. 2015

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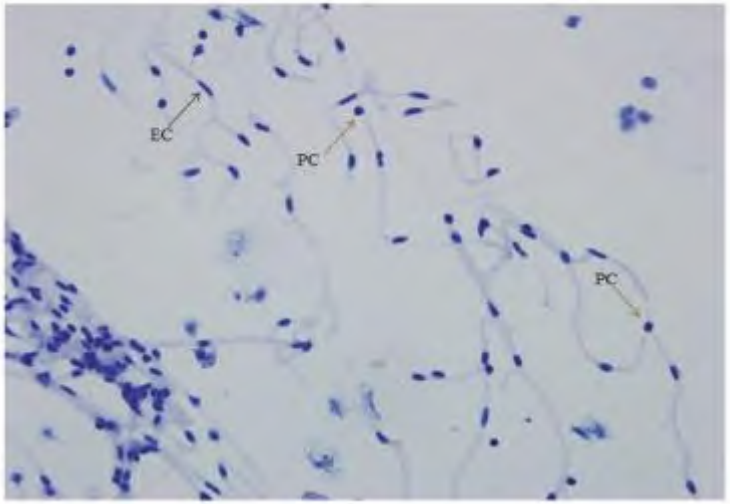

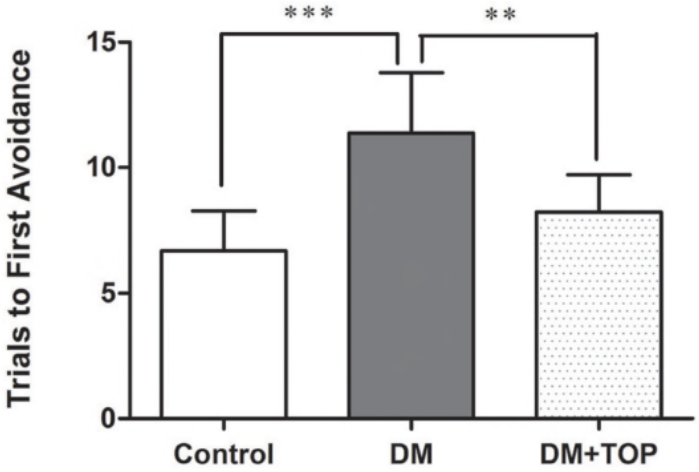

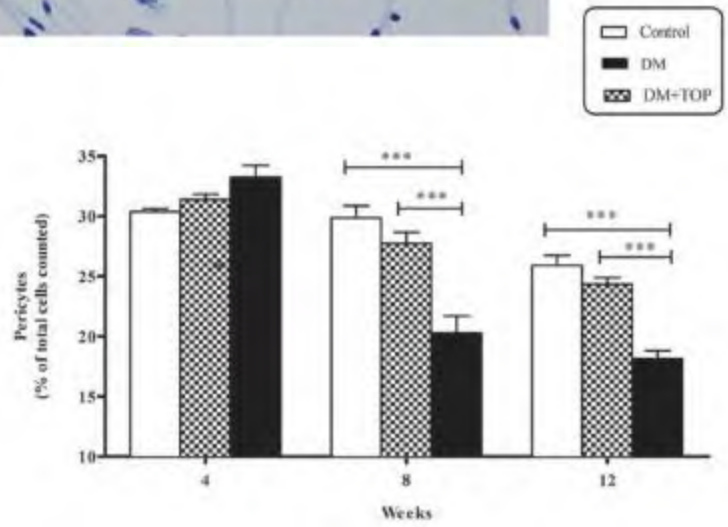

In conclusion, these data clearly demonstrate that topiramate at 1.0 mg/kg protects the mouse brain from diabetic damage. A 1.0 mg/kg topiramate in the mouse translates to a 5.0 mg daily dose in a 60 kg human, which may help slow the onset and progression of diabetic complications in the human brain.

Price TO et al., Int Libr Diabetes Metab. 2015

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Blood–Brain Barrier Disruption and Neurovascular Unit Dysfunction in Diabetic Mice: Protection with the Mitochondrial Carbonic Anhydrase Inhibitor Topiramate

Therese S. Salameh, Gul N. Shah, Tulin O. Price, Melvin R. Hayden, and William A. Banks

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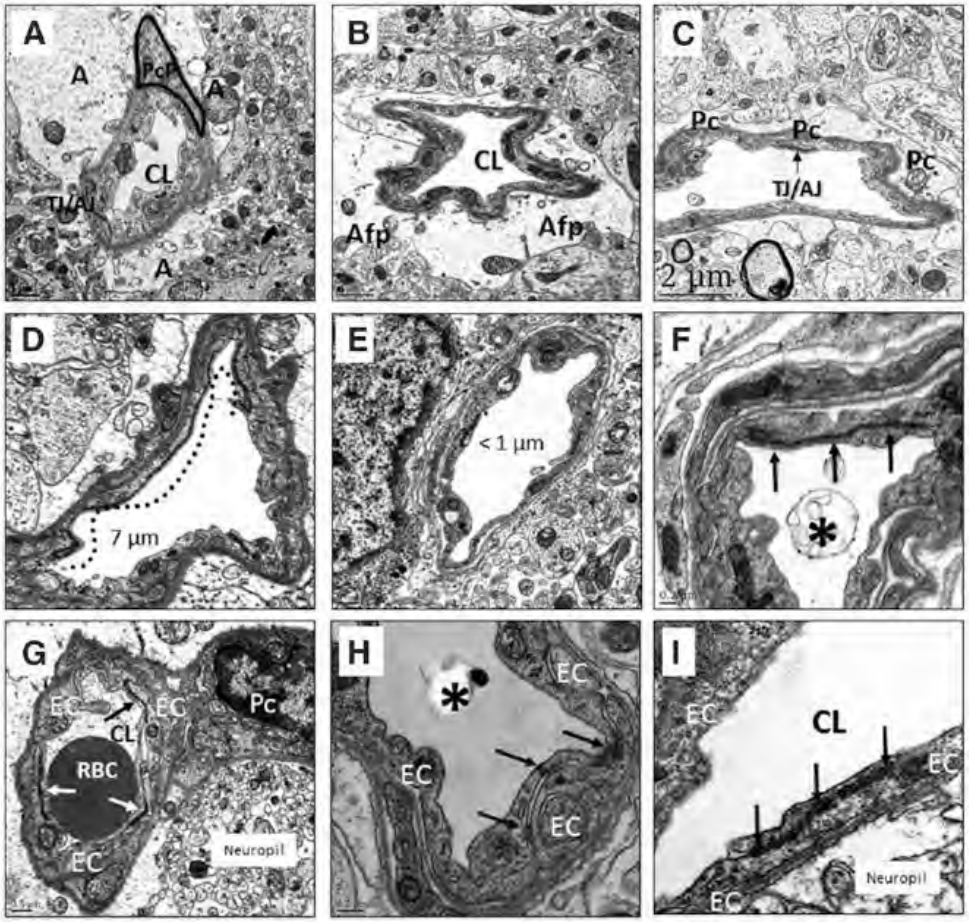

Fig. 5. Topiramate treatment protects pericytes, astrocytes, and BBB tight junctions from diabetes-induced damage. Electron micrographs of the midbrain of control (saline-treated: A, D, G), STZ-induced diabetic (B, E, and H), and TPM-treated STZ-induced diabetic mice (C, F, and I). (A) Control mice show normal possessing astrocytes, pericytes, and tight junctions/adherens junctions. Original magnification, 2500×; scale bar: 1 µm. (B) Mice with STZ-induced diabetes show loss of pericytes and an attenuation/loss of TJ/AJ. Original magnification, 2500×; scale bar: 1 µm. (C) Topiramate-treated STZ-induced diabetic mice showed normal pericytes and tight junctions/adherens junctions. In A and C, note the close relation of pericytes and astrocytes to endothelial cells. Original magnification, 2500×; scale bar: 2 µm. (D, G) Control mice show electron-dense elongated tight junctions/adherens junctions. Original magnification, 3000×; scale bar: 0.5 µm. (E, H) Tight junctions/adherens junctions are truncated in the STZ-induced diabetic mice. *E:* Original magnification, 3000×; scale bar: 0.5 µm. *I:* Original magnification, 10,000×; scale bar: 0.2 µm. (F, I) Treatment of STZ-induced diabetic mice with topiramate protected tight junctions/adherens junctions' length and increased electron density. *F:* Original magnification, 6000×; scale bar: 0.2 µm. *G* Original magnification, 3000×; scale bar: 0.5 µm. *H* Original magnification, 10,000×; scale bar: 0.2 µm. A, astrocytes; Afp, astrocyte foot process; AJ, adherens junctions; Asterisks, ghost RBC membranes within the capillaries; CL, capillary lumen; EC, endothelial cell; Pc, pericyte; RBC, red blood cell; TJ, tight junctions; TPM, topiramate.

Salameh TS et al., J Pharmacol Exp Ther, 2015

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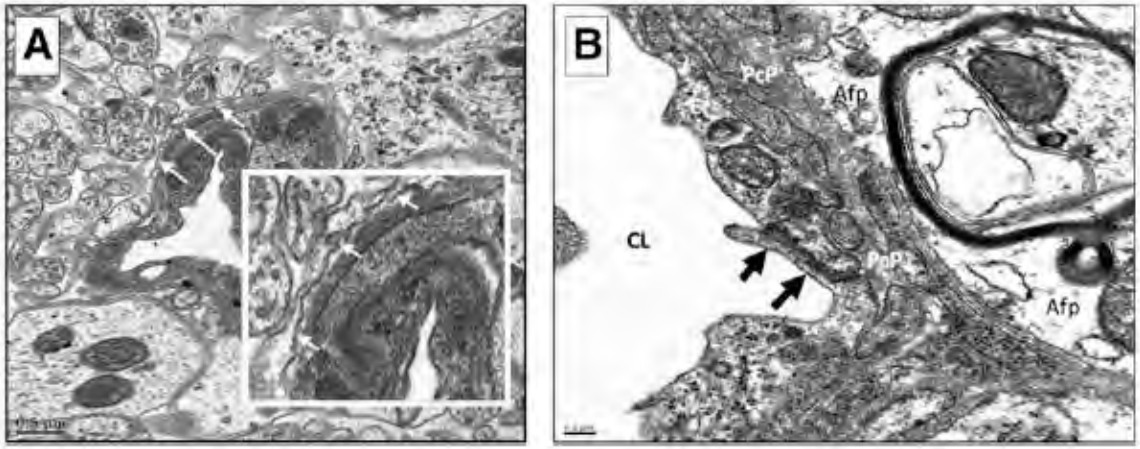

Fig. 6. Topiramate treatment protects astrocytes from diabetes-related membrane ruffling and maintains neurovascular unit (NVU) architecture in midbrain. (A) Ruffled membranes in astrocytes (white arrows) in the midbrain of STZ-induced diabetic mice. Insert: enlargement of A. Ruffling was not observed in control or topiramate-treated groups. Original magnification, 4000×; scale bar: 0.5 μm. (B) Normal NVU architecture with preserved relations among pericytes, astrocytes, and neurons in topiramate-treated STZ-induced diabetic mice. CL, capillary lumen. Original magnification, 5000×; scale bar = 0.2 μm.

In this study, we have demonstrated that

1. streptozotocin–induced diabetes resulted in BBB disruption,
2. ultrastructural studies showed a breakdown of the BBB and changes to the neurovascular unit (NVU), including a loss of brain pericytes and retraction of astrocytes, the two cell types that maintain the BBB
3. treatment with topiramate, a mCAi, attenuated the effects of diabetes on BBB disruption and ultrastructural changes in the neurovascular unit.

Salameh TS et al., J Pharmacol Exp Ther, 2015

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Regulation of high glucose-induced apoptosis of brain pericytes by mitochondrial CA VA: A specific target for prevention of diabetic cerebrovascular pathology

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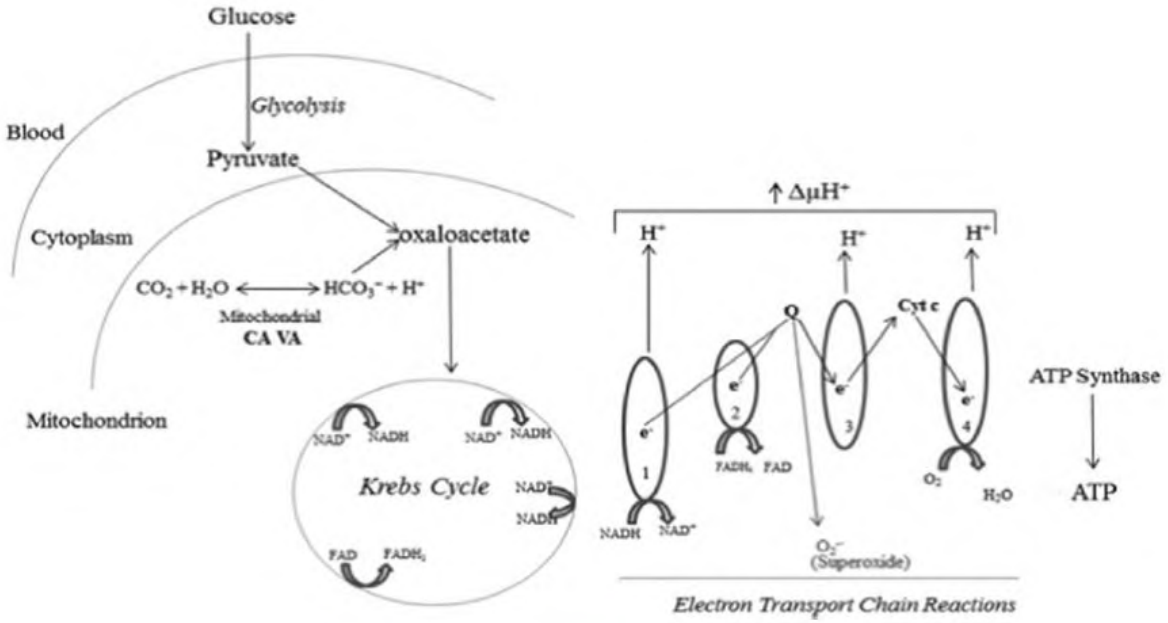
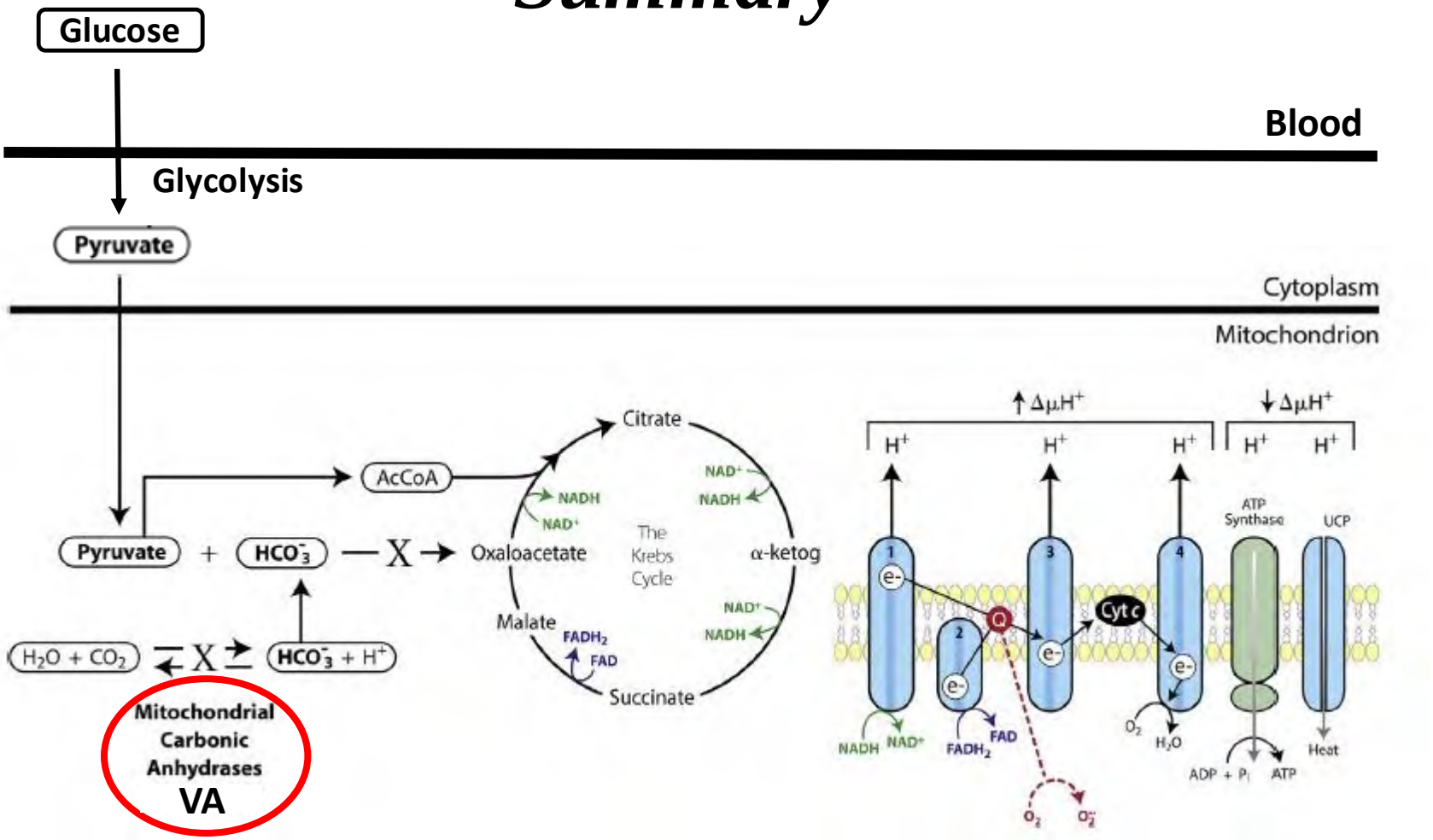


Fig. 7. Role of mitochondrial CA in ROS production and apoptosis in brain pericytes.

In this report, genetic knockdown and overexpression studies confirm that mitochondrial CA VA regulates respiration in pericytes, whereas mitochondrial CA VB does not contribute significantly.
Identification of mitochondrial CA VA as a sole regulator of respiration provides a specific target to develop new drugs with fewer side effects that may be better tolerated and can protect the brain from diabetic injury.
Since similar events occur in the capillary beds of other insulin-insensitive tissues such as the eye and kidney, these drugs may also slow the onset and progression of diabetic disease in these tissues.

Summary



糖尿病における脳微小血管障害の発症・進展を予防する一つの治療選択肢として、ペリサイトのミトコンドリア炭酸脱水素酵素を阻害する戦略がある