Microvascular disease: The Wrong Targets?

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Disclosures

- Speaker for GSK, Astra Zeneca, Takeda, Medicines Company, Merck, Novo Nordisk
- Advisory boards for Amgen, Novartis, Novo Nordisk, Astra Zeneca
- Diabetes adviser, Synexus
- Editor in Chief, Diabetes and Vascular Disease Research
- Co-chair ESC/EASD guidelines on CVD in Diabetes 2007-20

Major Vascular Complications of Diabetes

Microvascular

Cognitive impairment[3]

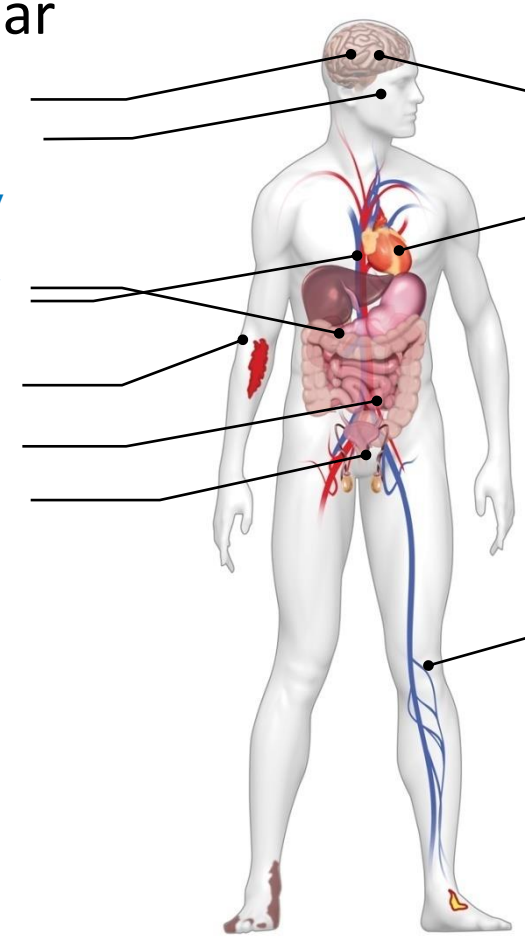
Diabetic retinopathy

Diabetic nephropathy

Diabetic neuropathy

Gastro-intestinal and bladder dysfunction

Sexual dysfunction



Macrovascular

Cerebrovascular disease

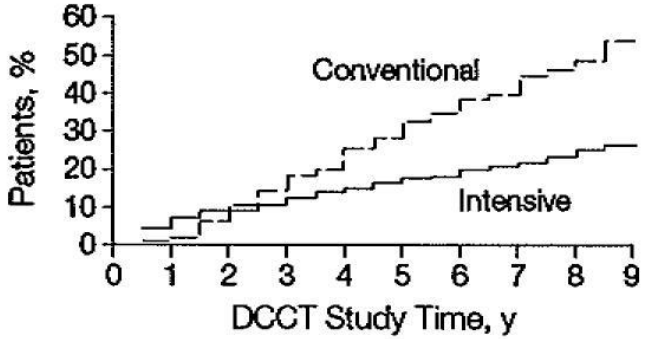
Coronary disease

Peripheral vascular disease

Adapted from: 1. International Diabetes Foundation. Time to Act: Type 2 diabetes, the metabolic syndrome and cardiovascular disease in Europe. 2006. 2. International Diabetes Federation. Time to Act. 2001. 3. Seaguist ER. Diabetes. 2010;59:4-6.

Long-term Microvascular Risk reduction in type 1 diabetes: DCCT-EDIC

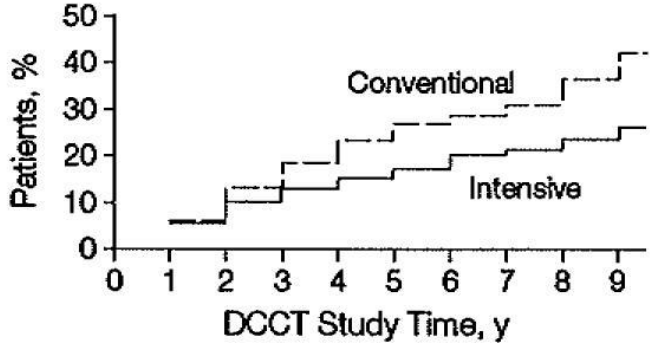
A Cumulative Incidence of Retinopathy Progression

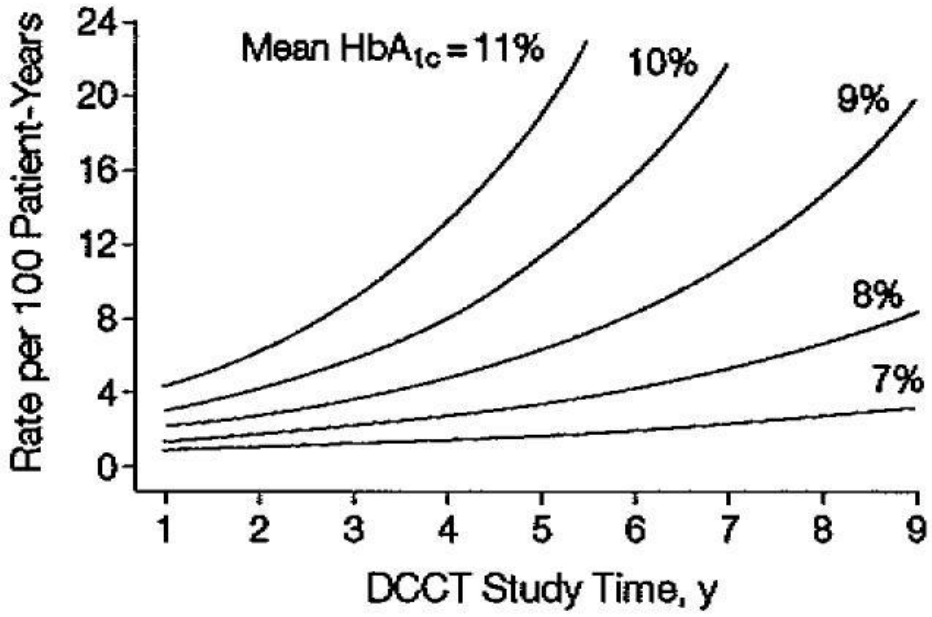


No. Evaluated

Conventional	352	349	351	348	345	324	211	128	83	78
Intensive	363	362	357	354	350	335	236	136	93	86

B Cumulative Incidence of Microalbuminuria





DCCT/EDIC Research Group. JAMA. 2002;287:2563-9.

Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus: A Systematic Review

Cochrane Library

- Reduced risk of *developing* microvascular complications;
  retinopathy: 73% $p < 0.00001$;
  nephropathy: 44% $p < 0.00001$;
  neuropathy: 65% $p < 0.00001$.

- Reduced risk of *progression* of retinopathy after at least two years 39% $p < 0.0001$;

- DCCT indicated intensive glucose control was highly cost-effective.

Fullerton B et al Cochrane Database Syst Reviews 201

Glucose-lowering studies confirmed benefit on microvascular complications but mixed results on macrovascular outcomes

Study[1]	Baseline HbA_{1c} Control vs intensive	Mean duration of diabetes at baseline (years)	Microvascular		CVD		Mortality	
UKPDS	9%→ 7.9% vs 7%	Newly diagnosed	↓	↓	↔	↓	↔	↓
ACCORD[1–3]	8.3%→ 7.5% vs 6.4%	10.0	↓*		↔		↑	
ADVANCE	7.5 %→ 7.3% vs 6.5%	8.0	↓	↔**	↔	↔	↔	↔
VADT	9.4 %→ 8.4% vs 6.9%	11.5	↓	?	↔	↓	↔	↔

Long-term follow-up[1,4,5]

*No change in primary microvascular composite but significant decreases in micro/macroalbuminuria[2,3]
**No change in major clinical microvascular events but significant reduction in ESRD (p = 0.007)[5]

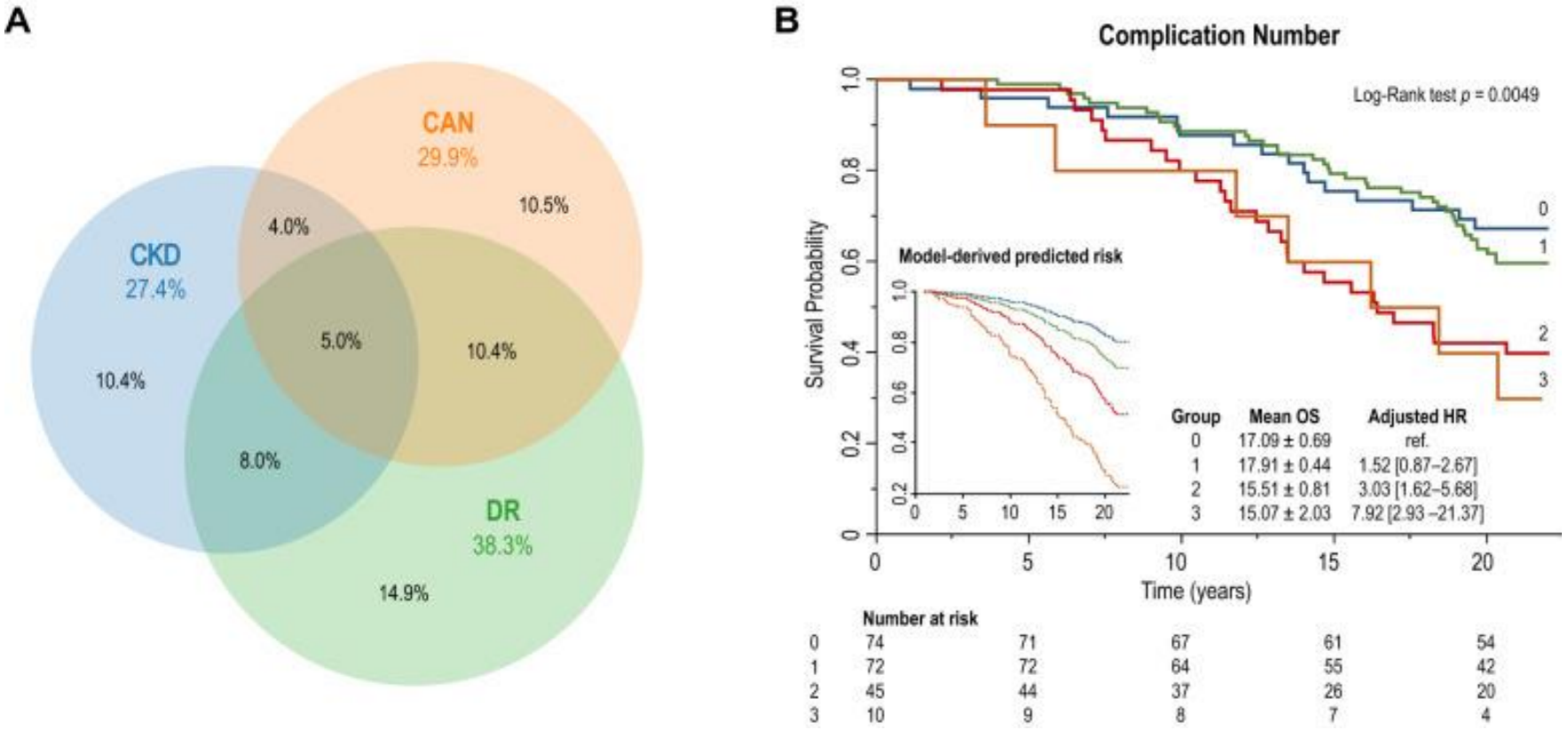
1. Table adapted from Bergenstal et al. Am J Med 2010;123:374.e9–e18. 2. Genuth et al. Clin Endocrinol Metab 2012;97:41–8.
3. Ismail-Beigi et al. Lancet 2010;376:419–30. 4. Hayward et al. N Engl J Med 2015;372:2197-206 (VADT). 5. Zoungas et al. N Engl J Med 2014;371:1392-406.

Glucose Targets for Preventing Diabetic Kidney Disease and its Progression

- Little or no difference to renal outcomes or cardiovascular mortality
- Probably lowers risk of onset and progression of microalbuminuria
- In 1,000 adults between zero and two people avoid non-fatal MI, seven avoid new-onset and two worsening albuminuria.
- The adverse effects of glycaemic management are uncertain.

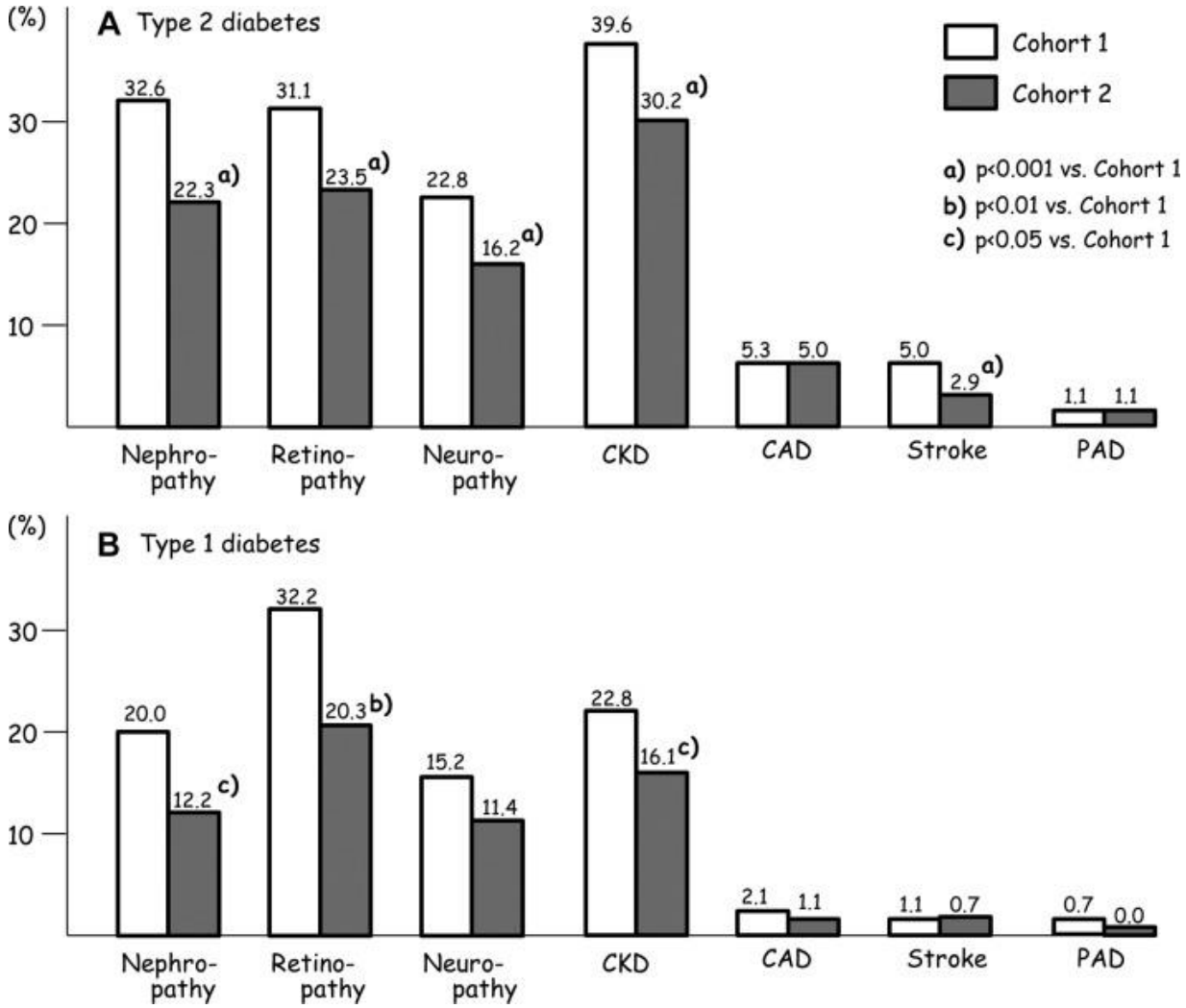
Ruospo M et al Cochrane database Syst Reviews 2017,

Synergistic effect of chronic kidney disease, neuropathy, and retinopathy on all-cause mortality in type 1 and type 2 diabetes: a 21-year longitudinal study



Suchetta L, et al Cardiovascular Diabetology 2022, 233-43

Declining Trends of Retinopathy and Nephropathy



Yokoyama H et al, BMJ open diabetes res care, 2018, 6.1

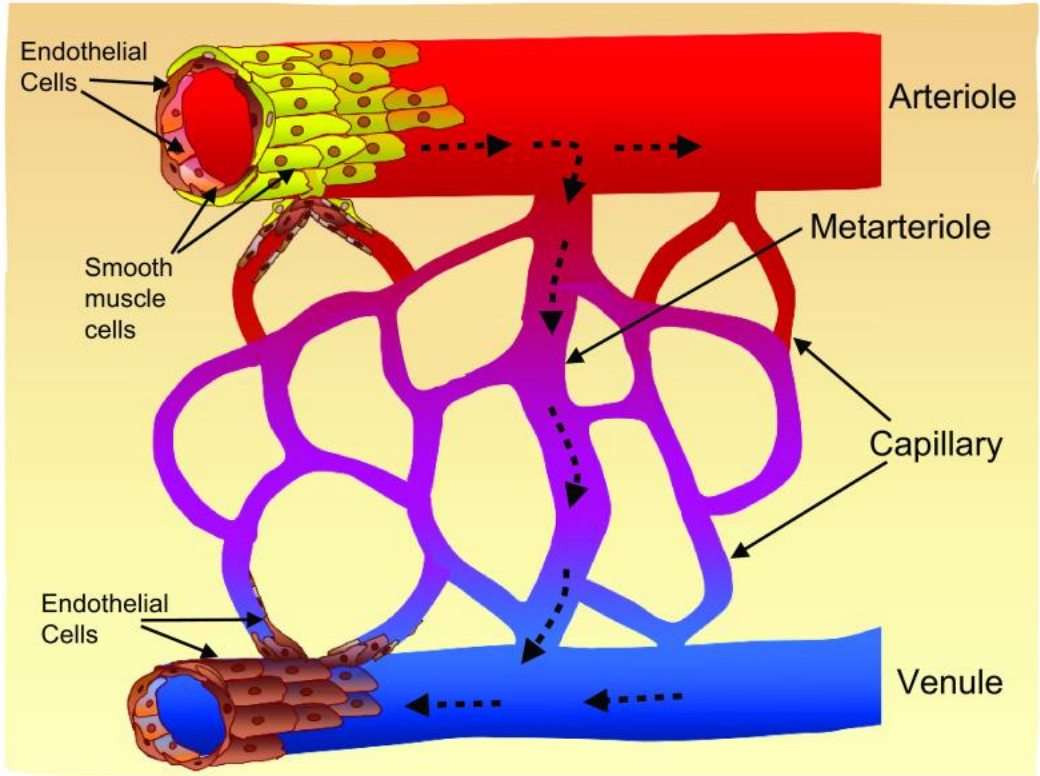
Microvascular disease: The Wrong Targets?

Target: An objective or result towards which efforts are directed.

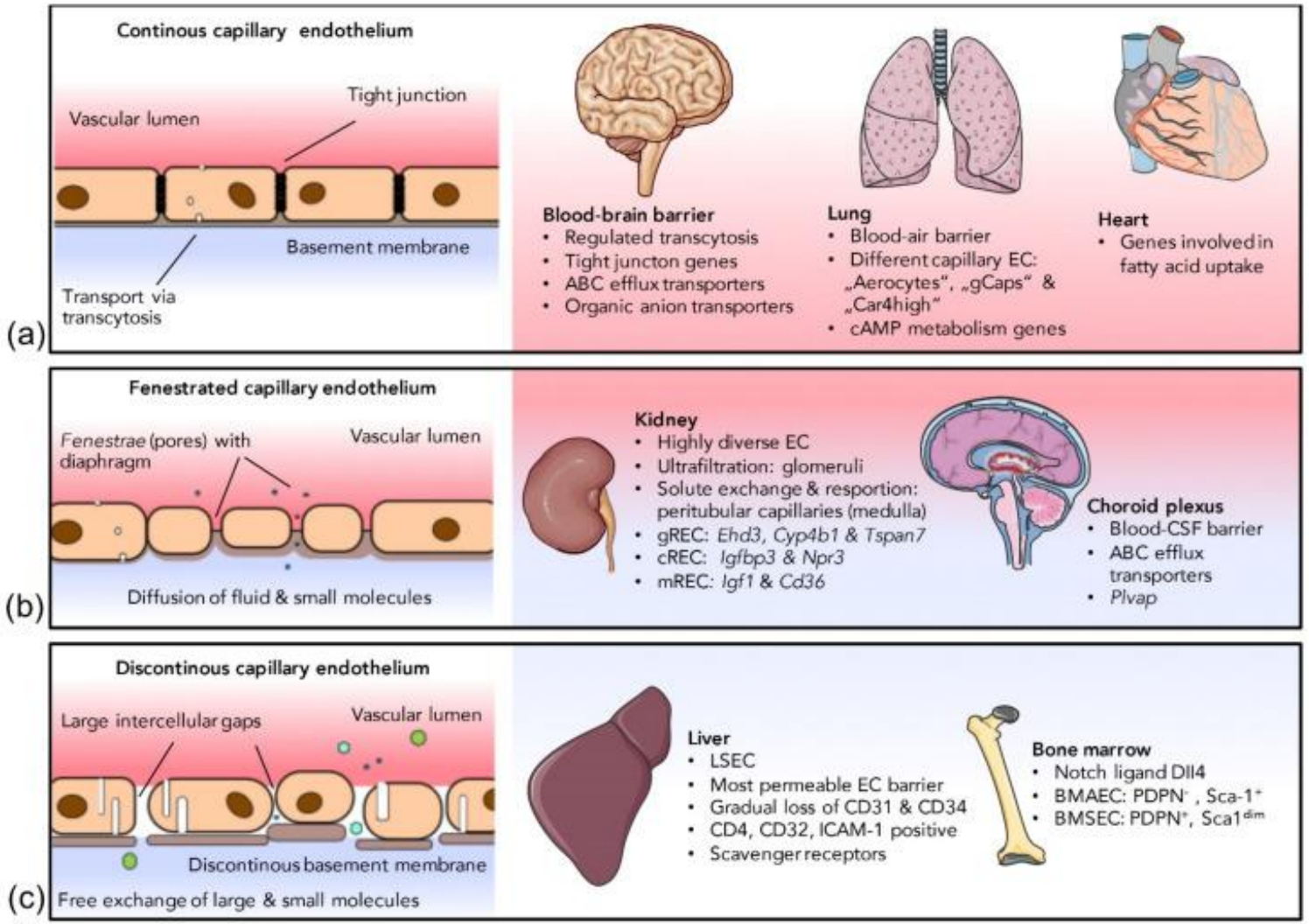
- Organs
  - Retinal Vasculature
  - Renal
  - Nerves
- Cells
  - Endothelium
  - Macrophages
- Molecules
  - Glucose
- Receptors
  - Insulin Receptor
  - SGLT2
  - GLP-1R

The Microvasculature

- Endothelial Cells line blood vessels from the aorta to microvessels, and form a selective blood-tissue barrier.
- Endothelium supports~60,000 miles of blood vessels.
- Endothelium cover 3,000 to 6,000 square metres of the human body.
- It includes at least 1 trillion endothelial cells
- Renal endothelial cells exhibit functions related to filtration while brain endothelial cells maintain the blood-brain-barrier as a vital mechanism of protection against harmful agents.
- Abnormalities of endothelial cell function are involved in a variety of vascular disorders

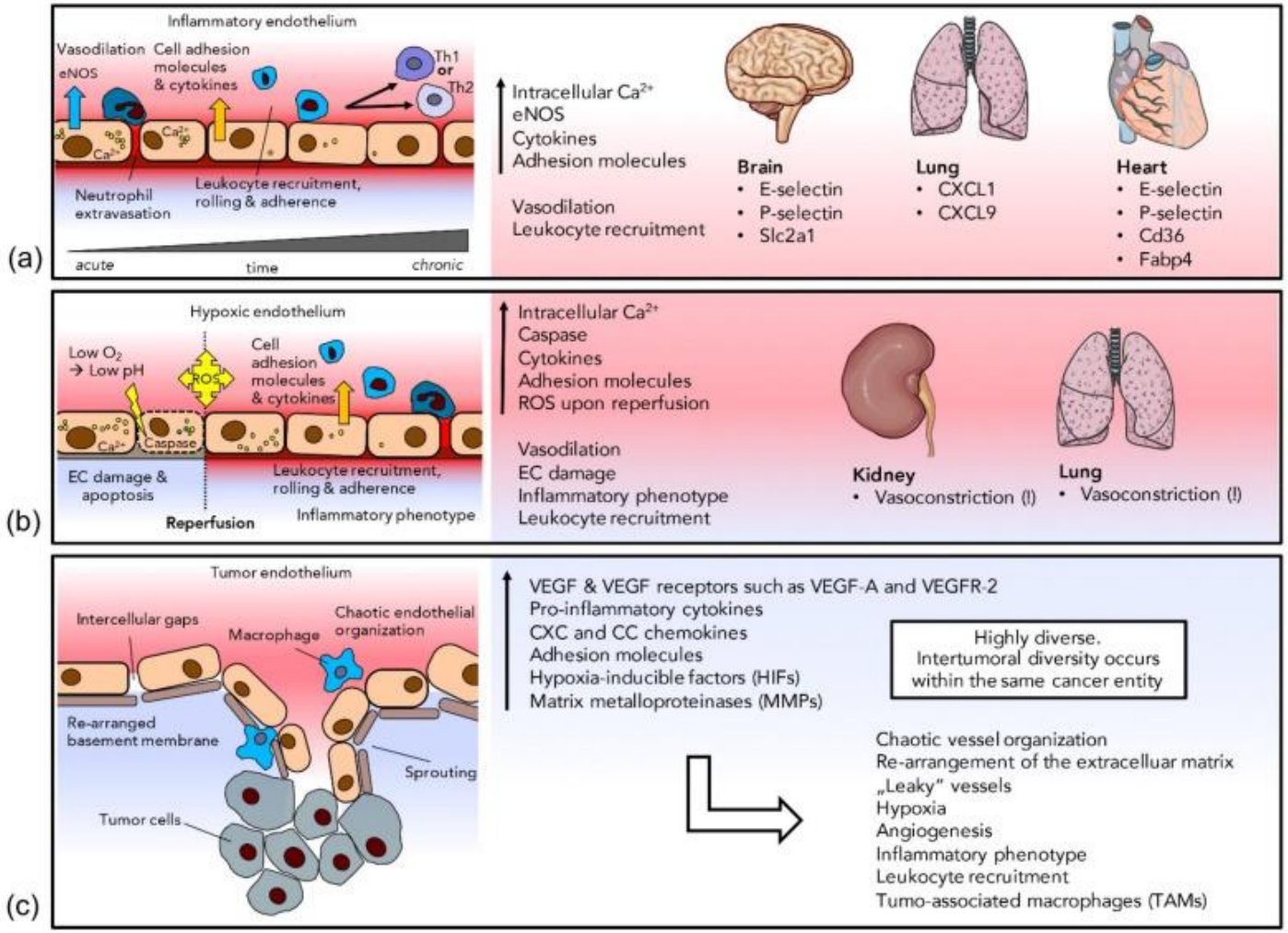


Heterogeneity of Endothelial Cells



Hennigs JK et al Cells 2021; 10, 2712

Heterogeneity of Endothelial Cell Responses

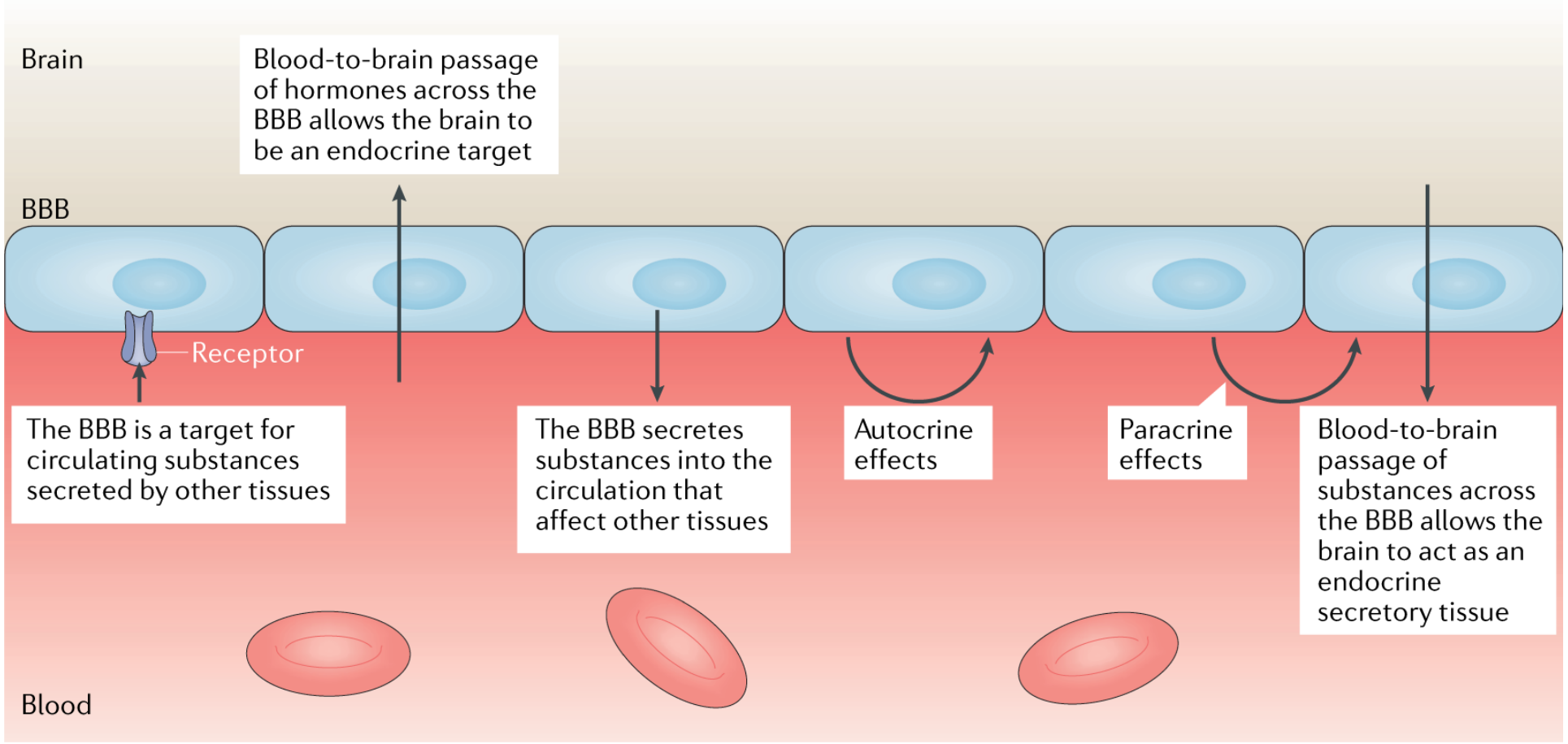


Hennigs JK et al Cells 2021; 10, 2712

Neurological Complications of Diabetes Mellitus

- Vascular dementia,
- Stroke,
- Anxiety/ depression and
- Cognitive impairment
- DM can aggravate epilepsy
- Diabetic encephalopathy increases the probability of cognitive decline, acceleration of Alzheimer's disease and other forms of dementia

The Blood Brain Barrier

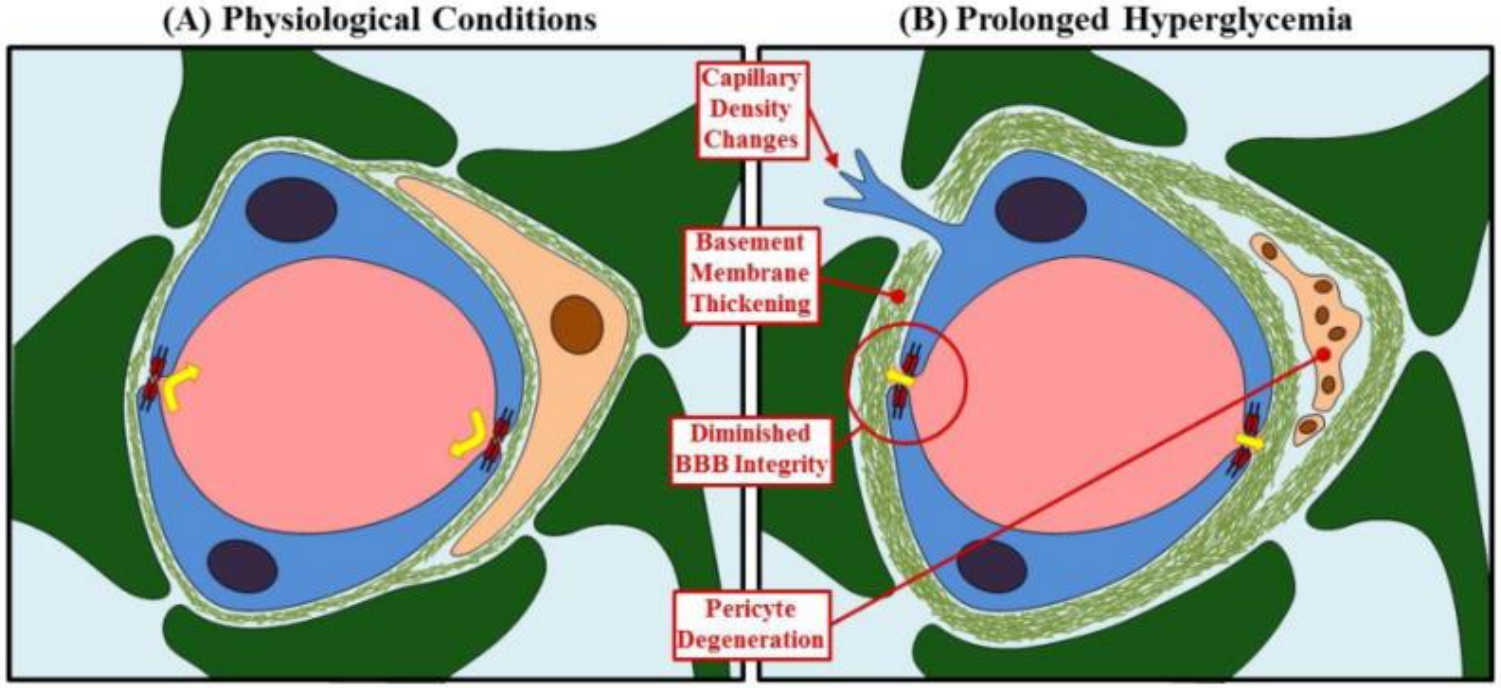


Effects of Diabetes on the Blood Brain Barrier

- Endothelial dysfunction
  Vascular damage, neurodegeneration

- Astrocyte dysfunction
  swollen end feet, detached membrane, increased permeability

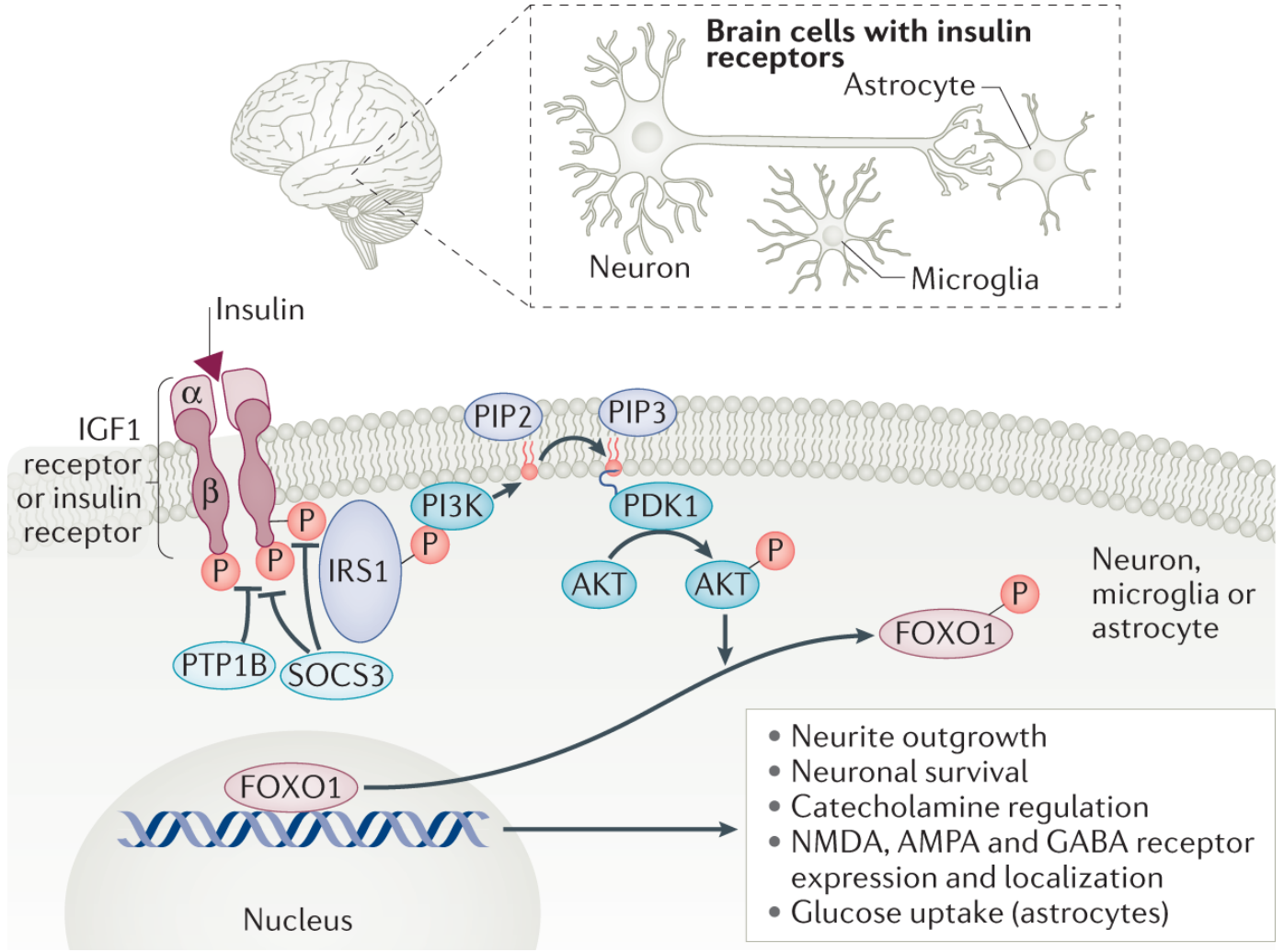
- Pericyte dysfunction
  micro aneurysms, haemorrhage, decreased capillary perfusion



Bogush M, Heldt NA, Persidsky Y J Neuroimmune Pharmacol 2017 593-601

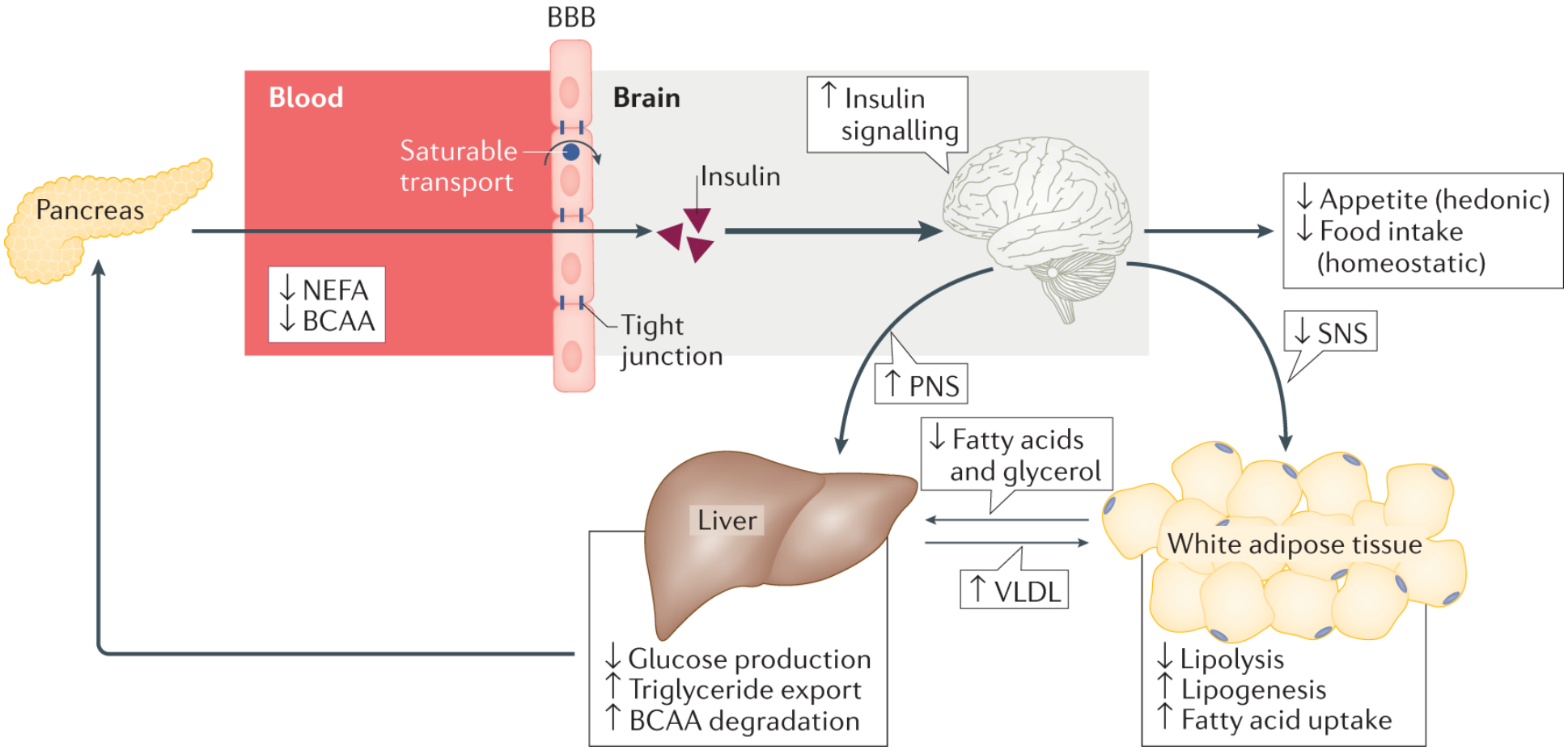
Brain insulin signalling cascade.

- Insulin crosses the blood–brain barrier to bind to insulin receptors widely expressed throughout the brain.
- Brain insulin controls appetite, adipose tissue lipolysis, hepatic triglyceride secretion and branched-chain amino acid metabolism, protecting the organism from ectopic lipid accumulation and lipotoxicity.
- Overnutrition rapidly induces brain insulin resistance before impaired peripheral insulin signalling, implicating brain insulin resistance as a key culprit of metabolic disease and diabetes.
- Interventions to improve brain insulin signalling have therapeutic potential for metabolic disease, diabetes and non-alcoholic fatty liver disease; augmenting brain insulin signalling might be particularly beneficial in preventing lipotoxicity with a low risk of hypoglycaemia.



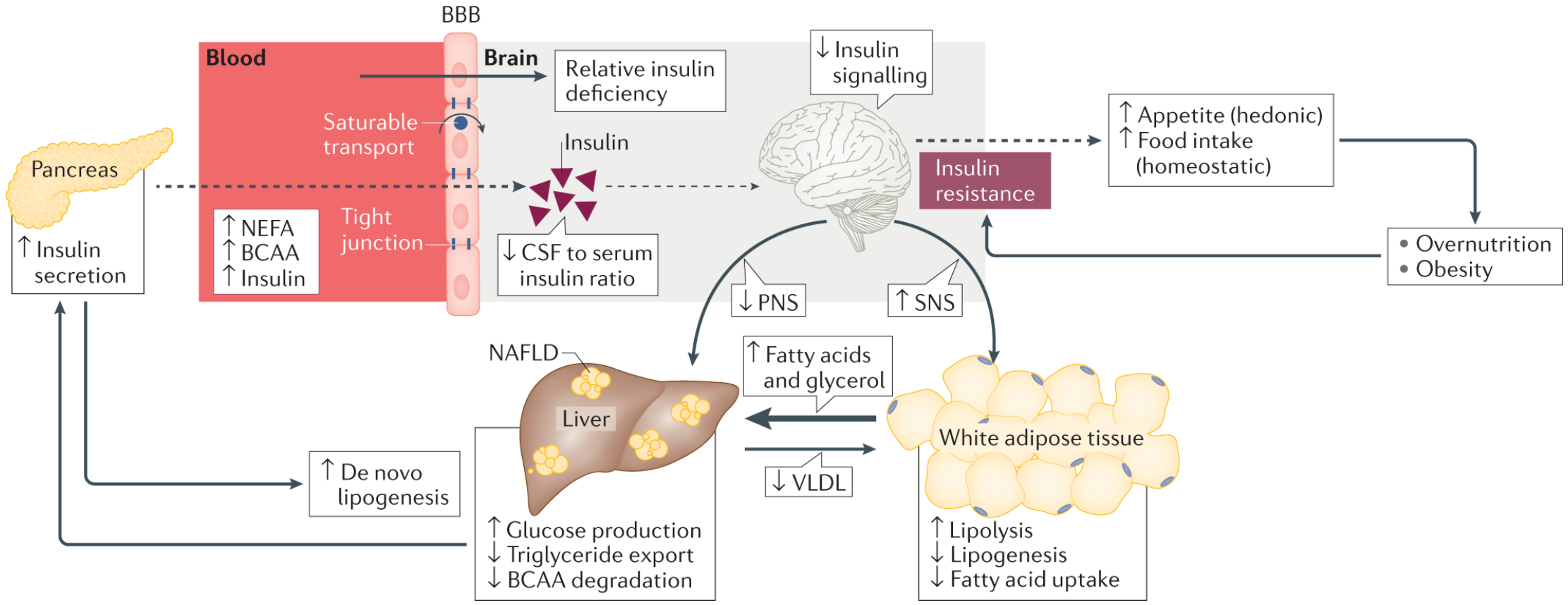
Scherer T, Sakamoto K, Buettner C, Nature Rev Endo 2021;17, 468-83

Physiological functions of brain insulin action.



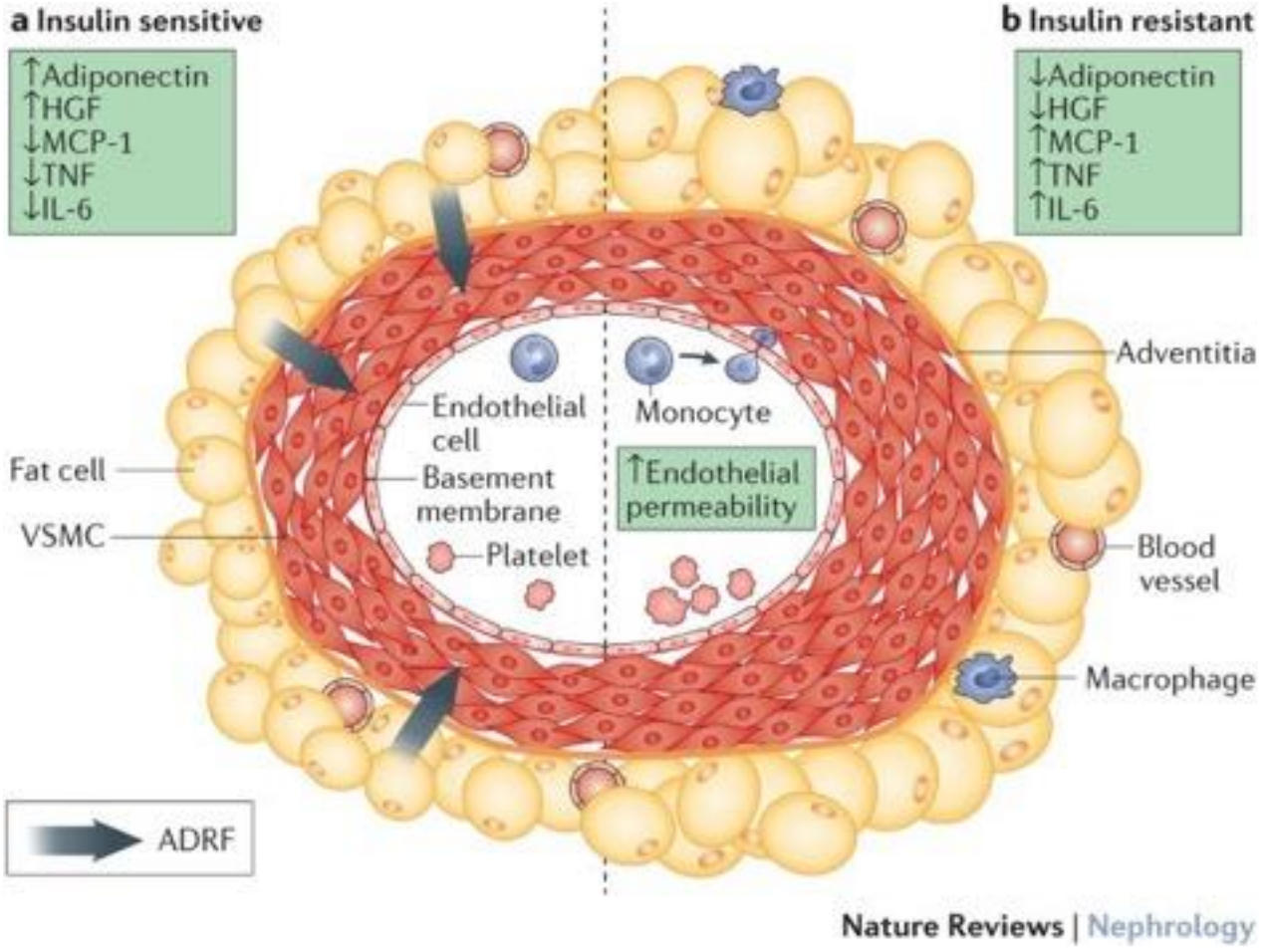
Scherer T, Sakamoto K, Buettner C, Nature Rev Endo 2021;17, 468-83

Brain insulin resistance and its metabolic sequelae.



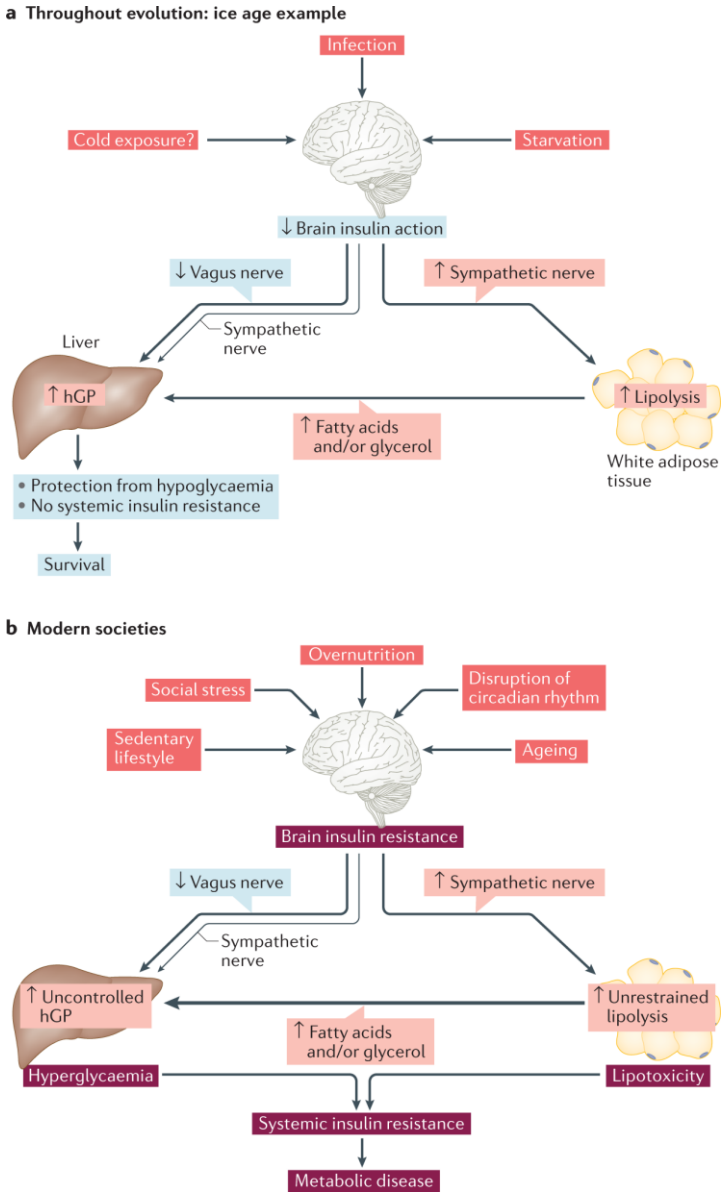
Scherer T, Sakamoto K, Buettner C, Nature Rev Endo 2021;17, 468-83

Perivascular adipose tissue influences vascular function.



Artunc F et al Nature Reviews Neph, 2016,12 721-37

An Evolutionary Advantage for Brain Insulin Resistance ?

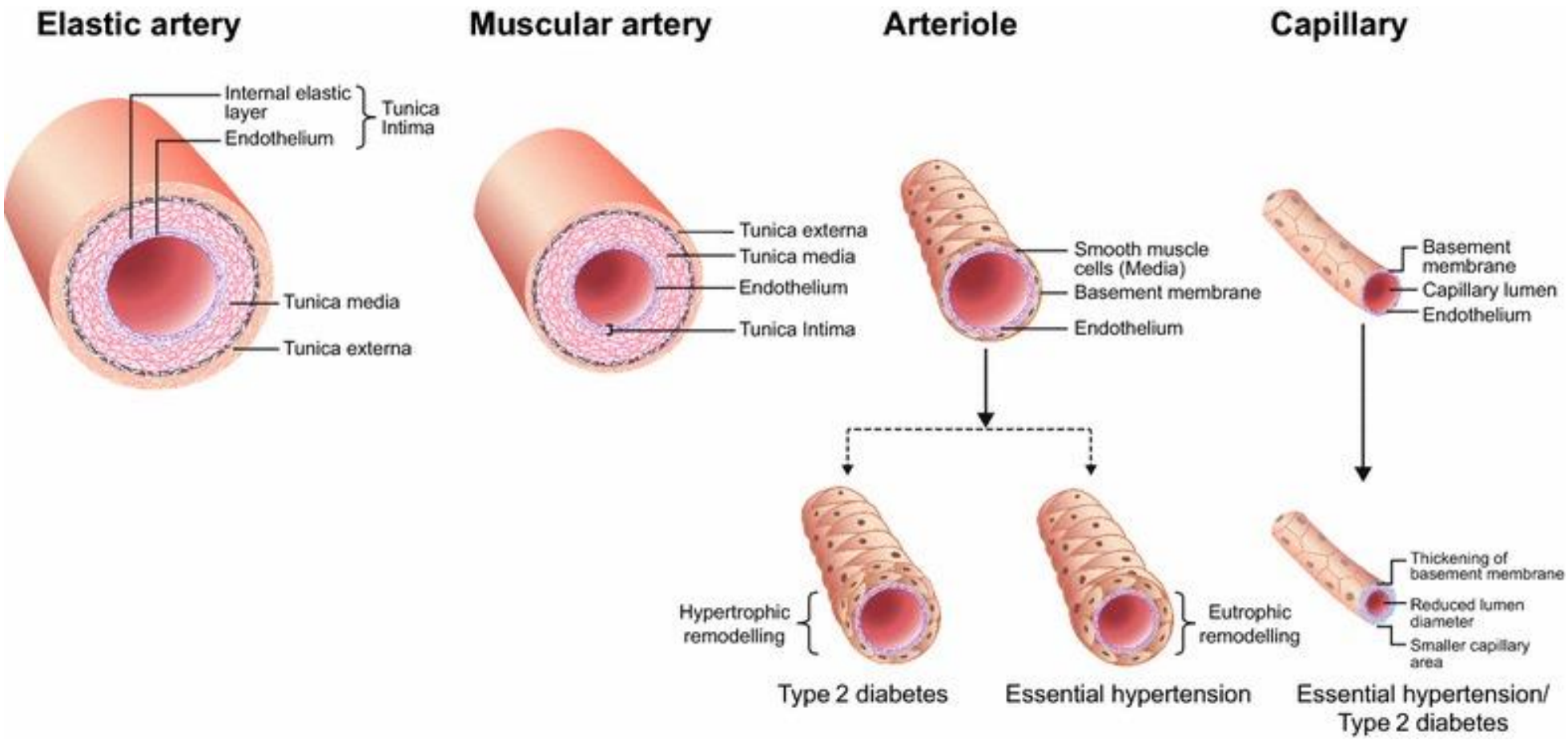


A In mammalian evolution, cold exposure, starvation and infection were a major cause of mortality. Brain insulin resistance can be understood as a physiological adaptation to maintain euglycaemia by increasing lipolysis in adipose tissue and augmenting hepatic glucose production, a process probably critical for survival when nutrients were scarce.

b | In modern societies, overnutrition and a sedentary lifestyle as well as social stress, disruption of circadian rhythmis and ageing, promote brain insulin resistance, which results in dysregulation of the autonomic nervous system, ectopic lipid deposition and glucolipotoxicity that fuels systemic insulin resistance.

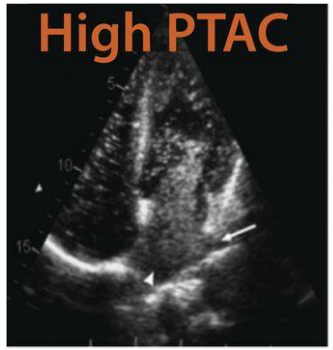
Scherer T, Sakamoto K, Buettner C, Nature Rev Endo 2021;17, 468-83

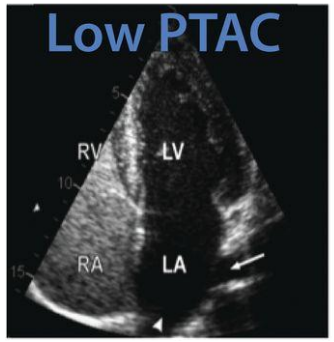
Diabetes and the Myocardial Microcirculation

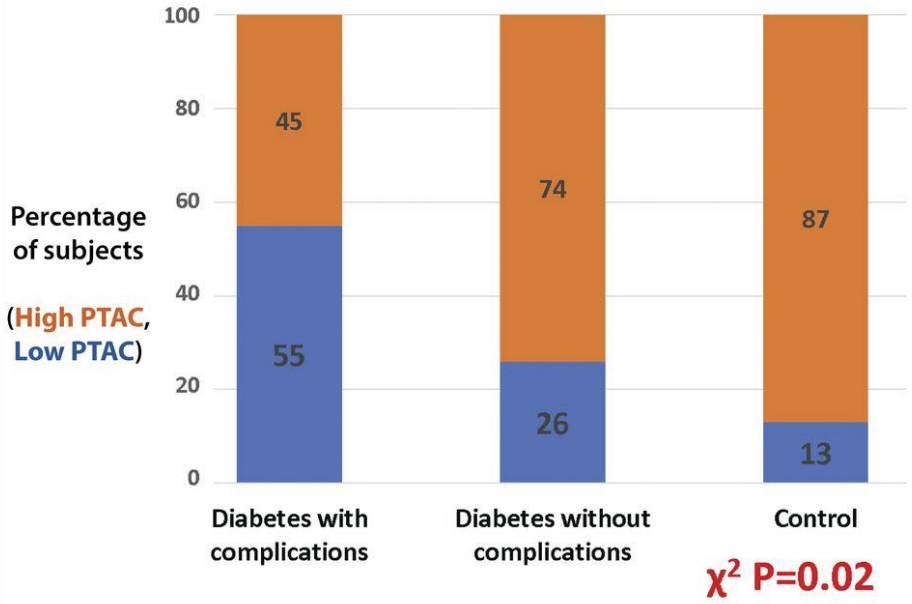


Strain WD et al , Cardiovascular Diabetology, 2018, 17, 57

Diagnosis and Significance of Pulmonary Microvascular Disease in Diabetes



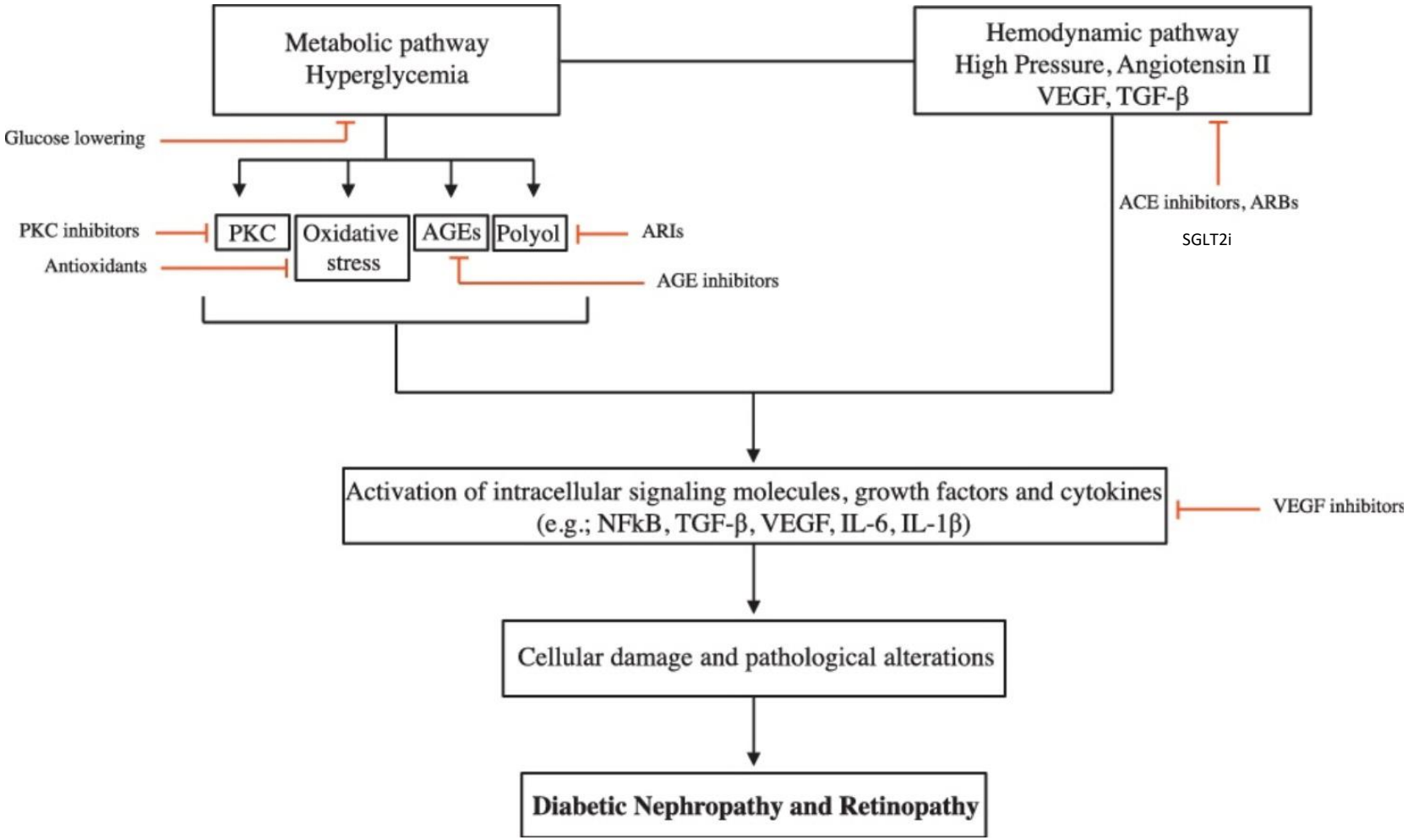




- Low PTAC was associated with a 24% lower VO_2peak (P = 0.006),
- Reduced right ventricular function (P = 0.015),
- Increased pulmonary artery pressures during exercise (P = 0.02).

Roberts TJ et al Diabetes Care 2018 Apr;41(4):854-861.

Therapeutic Approaches to Microvascular Disease



Usuelli, V, Pharmacological Research 98 (2015) 39–44

Summary and Conclusions

- Vascular endothelial cells (EC) comprise the largest endocrine organ
- Structural and functional heterogeneity of EC's is largely determined by their anatomical distribution
- In the kidney ECs are supported by podocytes, in the blood brain barrier by pericytes and astrocytes.
- In diabetes, most microvascular beds function abnormally, creating organ related morbidity and mortality
- Novel therapeutic approaches, perhaps related to tissue specific EC gene expression may be more appropriate for a 'holistic' approach to the widespread microvascular complications of diabetes.