

ACADEMIA LATINOAMERICANA
DE MEDICINA DEL ADULTO MAYOR
ALMA

Neuropatía Diabética
Fisiopatología

Grupo 4

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Definición

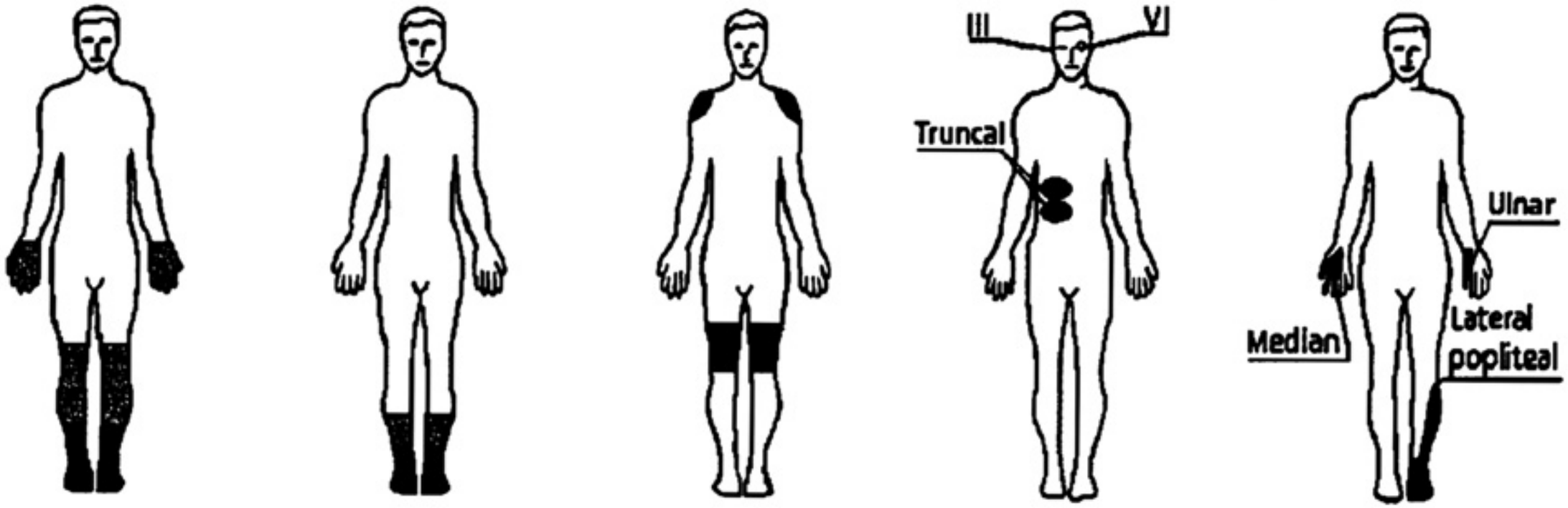
- Signos y síntomas de disfunción neuronal periférica en pacientes diabéticos, en quienes se ha descartado otra causa de neuropatía.

- Enf. caracterizada por una pérdida progresiva de fibras nerviosas que llevan a pérdida de la sensibilidad, ulceraciones en pies y amputaciones. OMS

- Puede afectar hasta un 30% de todos los diabéticos, y es el principal factor inicial del pie diabético.

Tesfaye S, et.al. Eurodiab IDDM, Diabetología 1996;39:1377-1384.

Neuropatía Diabética



Large fiber Neuropathy	Small fiber Neuropathy	Proximal motor Neuropathy	Acute mono Neuropathies	Pressure Palsies
Sensory loss: 0→ +++ (Touch, vibration) Pain: + → +++ Tendon reflex: N → ↓↓↓ Motor deficit 0 → +++	Sensory loss: 0 → + (thermal , allodynia) Pain: + → +++ . Tendon reflex: N → ↓ Motor deficit: 0	Sensory loss: 0 → + Pain: + → +++ Tendon reflex: ↓↓ Proximal Motor deficit: + → +++.	Sensory loss: 0 → + Pain: + → +++ Tendon reflex: N Motor deficit: + → +++	Sensory loss in Nerve distribution: + → +++ Pain: + → ++ Tendon reflex: N Motor deficit: + → +++

Different clinical presentations of diabetic neuropathy. (From Vinik AI, Park TS, Stansberry KB, et al. Diabetologia 2000;43:960;

Fisiopatologia

- El efecto deletéreo de la glucosa ha sido demostrado en el estudio Diabetes Control and Complications Trial
  - La hiperglicemia y el déficit insulínico contribuyen al desarrollo y progresión de la ND
  - La reducción de glicemia disminuye el riesgo de ND en 60% a 5 años
- La etiología se piensa que es multifactorial y hay diversas teorías

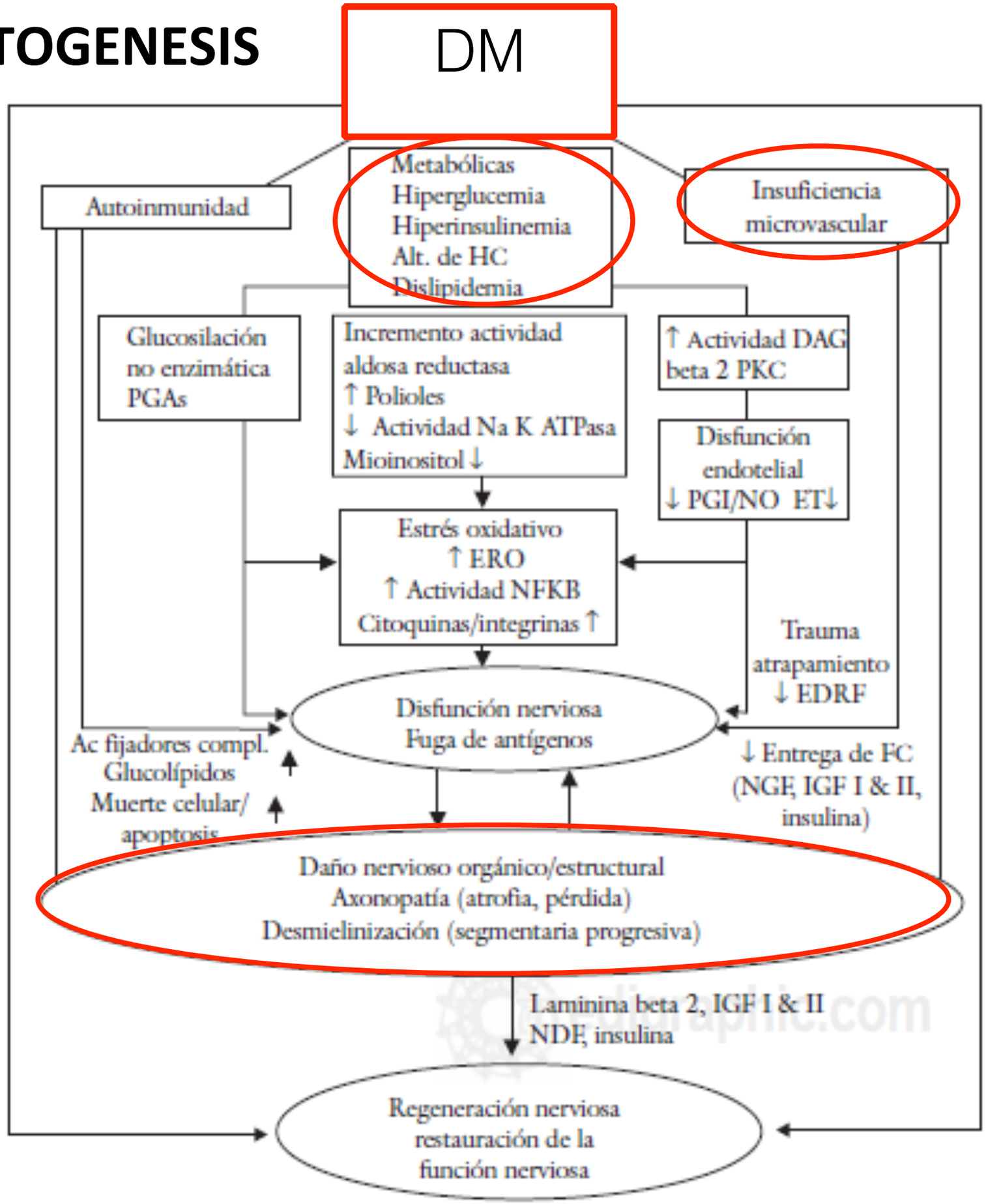
Etiología

- Metabólica
- Autoimmune
- Inflamación
- Vascular

- Hiperglicemia crónica
- Disfunción microvascular del nervio
- Estrés oxidativo
- Hiperactividad de la vía de los Polioles
- Hiperactividad de la PKC
- Glicación no enzimática
- Deficiencia de factores de crecimiento neurohumoral

Different clinical presentations of diabetic neuropathy. (From Vinik AI, Park TS, Stansberry KB, et al. Diabetologia 2000;43:960;

PATOGENESIS



PGA producto de la glucosilación avanzada
PKC proteinkinasa C
PG1 prostaglandina 1
NO oxido nitrico
FDRF factor relajador derivado del endotelio
NGF factor de crecimiento nervioso
IGF factor de crecimiento de tipo insulinico
ERO especies reactivas de oxigeno
NFKB factor nuclear kappa, beta

TEORIA METABOLICA

Hiperglicemia neuronal

Vía de los polioles

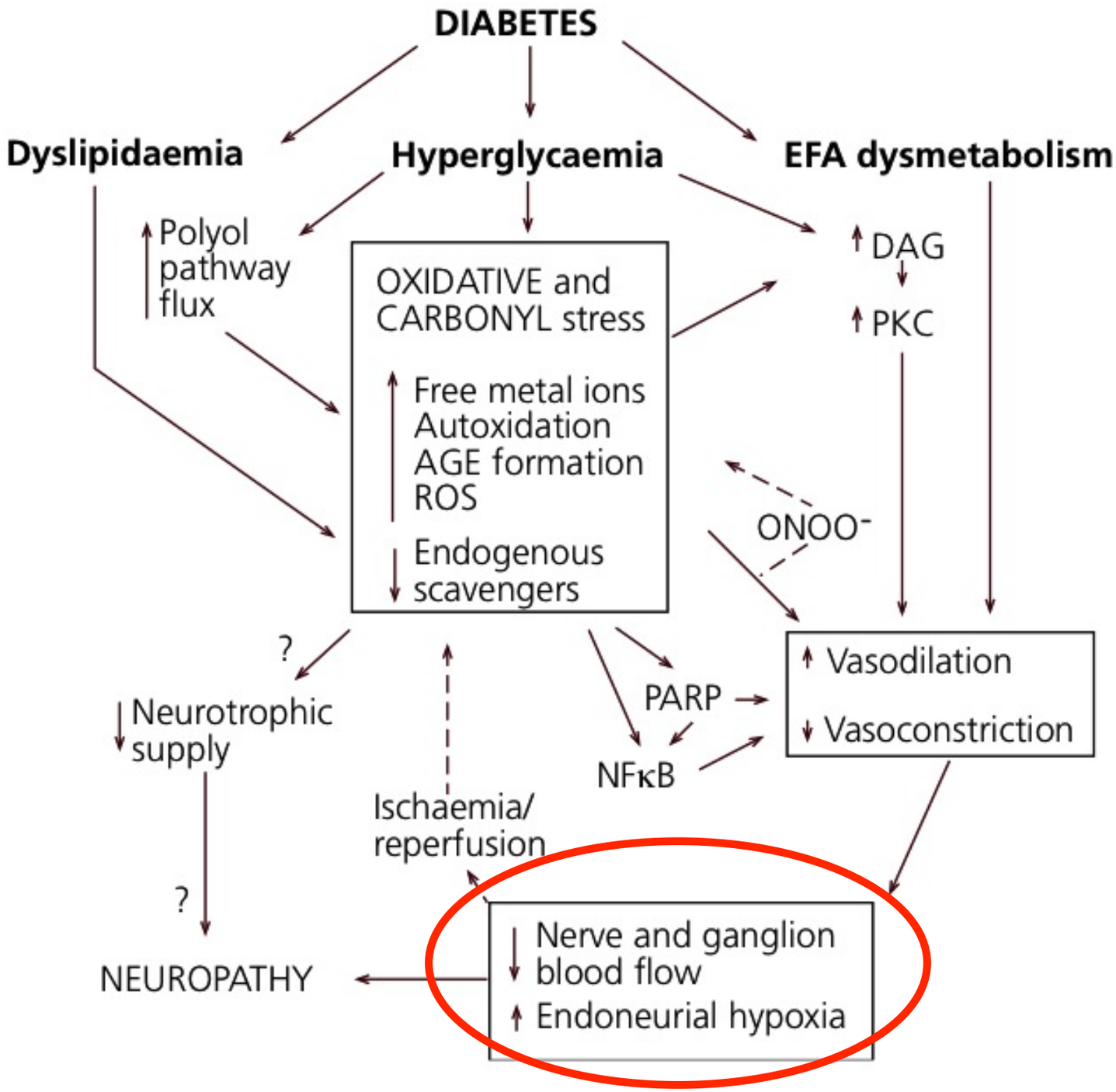
Mayor estrés oxidativo
Menor actividad de la Na^+/K^+-ATPasa

Disminución del transporte axonal
Daño estructural neural

Propagación anormal del potencial de acción

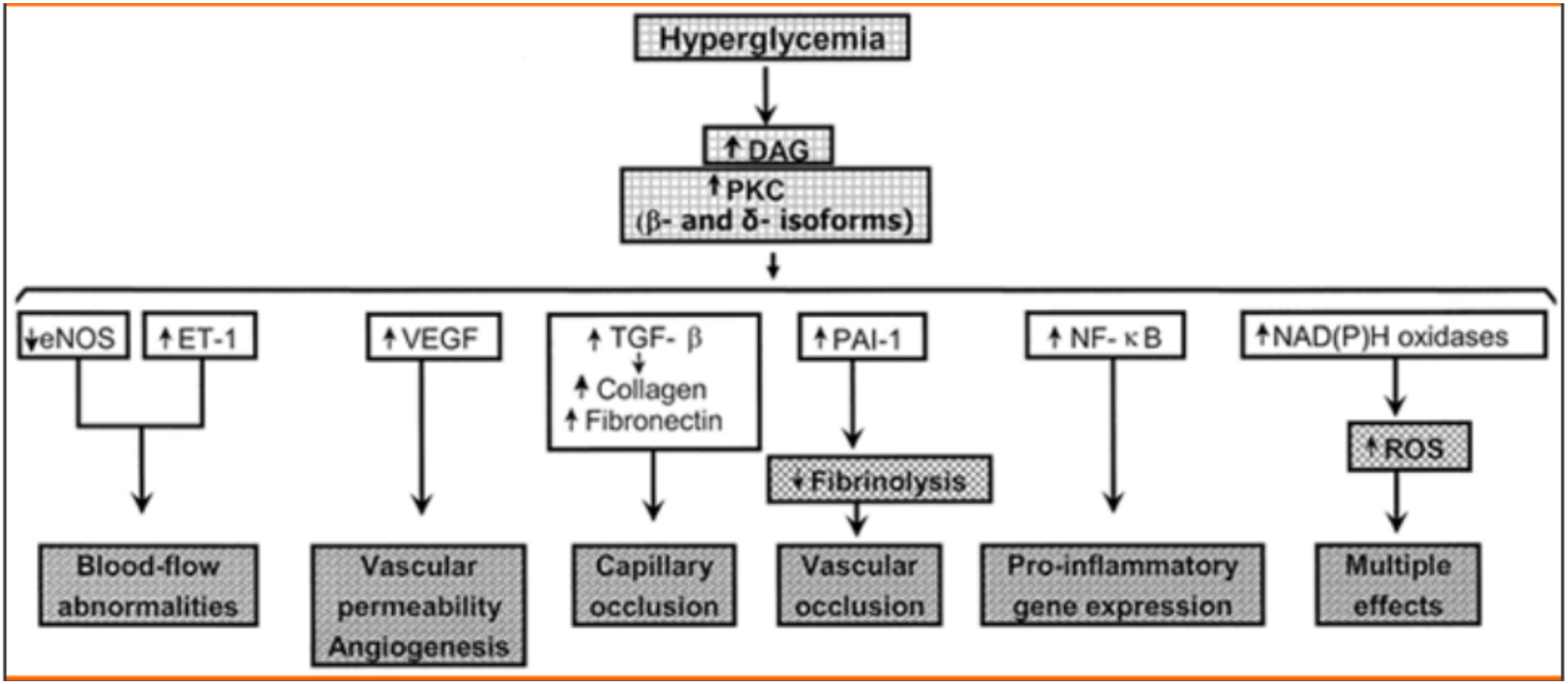
Quan D. Rev Cubana Angiol y Cir Vasc 2001;2(2):131-41.

Teroría Metabólica Vascular



Cameron NE, Eaton SEM, Cotter MA, et al. Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. Diabetologia 2001;44:1973–88

PKC


Hyperglycemia
↑DAG
↑PKC
(β- and δ- isoforms)
↓eNOS
↑ET-1
↑VEGF
↑TGF- β
↑Collagen
↑Fibronectin
↑PAI-1
↑NF- κB
↑NAD(P)H oxidases
↑ROS
↓Fibrinolysis
Blood-flow abnormalities
Vascular permeability Angiogenesis
Capillary occlusion
Vascular occlusion
Pro-inflammatory gene expression
Multiple effects

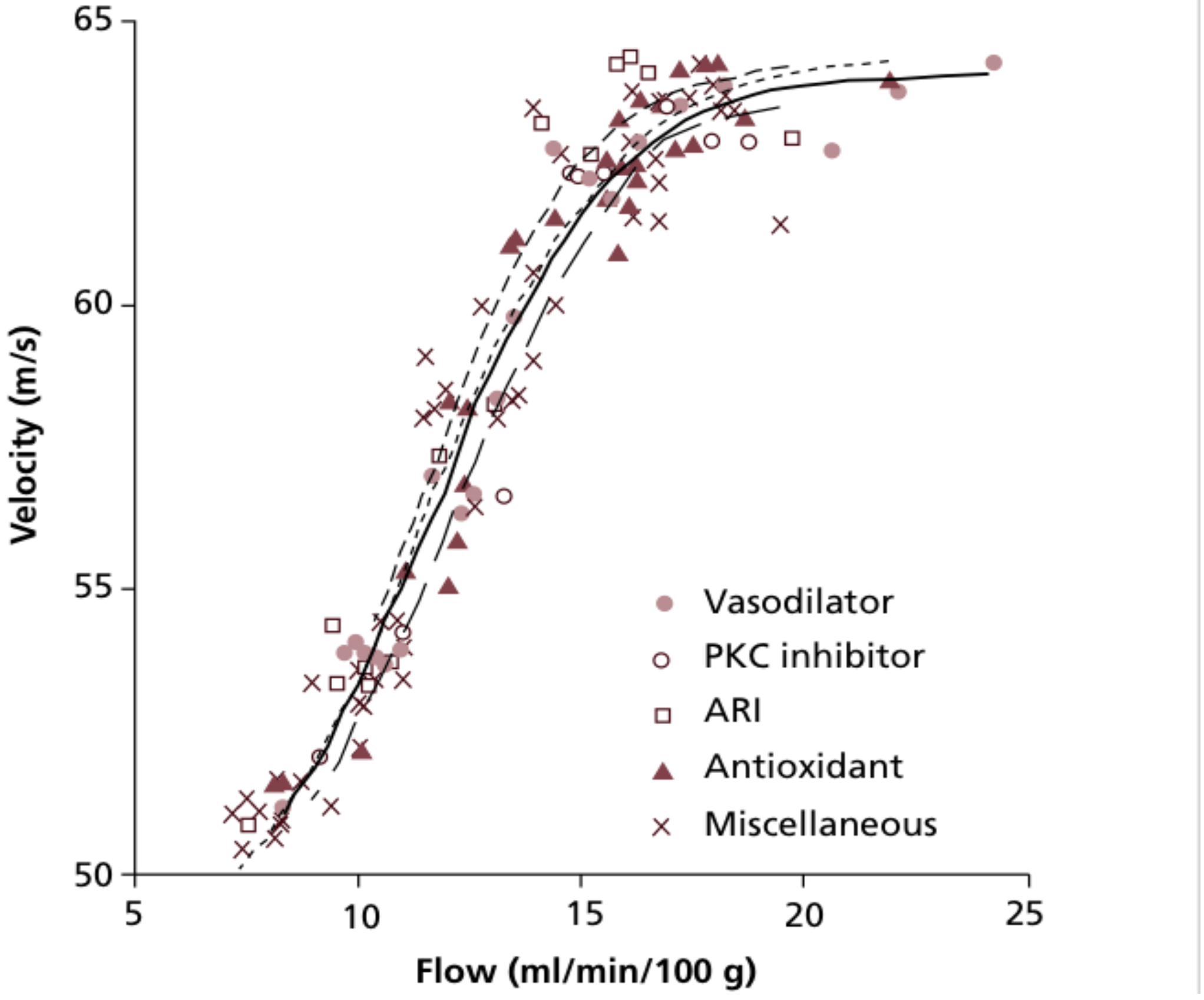
Teoría vascular

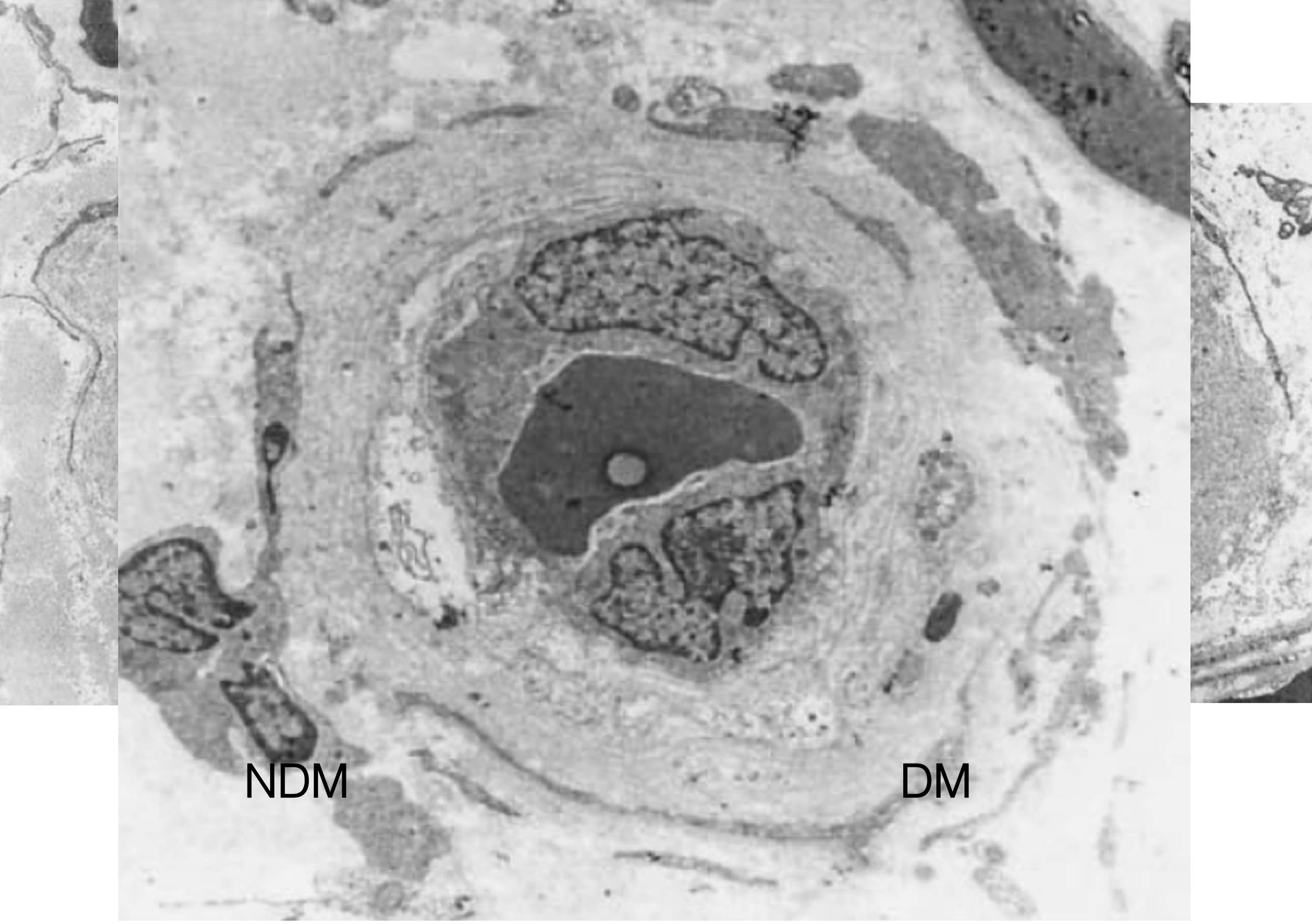
Estudios experimentales

Key messages

- The major cause of experimental diabetic neuropathy is impaired nerve blood flow, leading to endoneurial hypoxia
- Vascular endothelium is the main target for multiple metabolic insults in diabetes, causing decreased vasodilation by nitric oxide, prostacyclin and endothelium-derived hyperpolarising factor, and increased vasa nervorum reactivity to vasoconstrictors
- A combination of hyperglycaemia, dyslipidaemia and hypoinsulinaemia results in elevated oxidative and carbonyl stress, which directly and through activation of cell signalling pathways impairs nerve perfusion

Factor microvascular





DM-DNP

Teoría de la alteración neurotrófica

- Los factores neurotróficos son importantes en el mantenimiento, desarrollo y regeneración a nivel del SNC.

- Factor de crecimiento neural (FCN) es el mas estudiado

- Estudios en animales con DM, tanto la producción como el transporte están alterados.

Quan D. University of Colorado Health Sciences Center . Sep 28, 2006.

Conclusión

La fisiopatología de la NPD esta asociada a factores metabólicos, e insuficiencia microvascular, los cuales llevan al daño nervioso órgano-estructural por diferentes vías fisiopatológicas, produciendo Axonopatías con atrofia o pérdida y Desmielinización segmental o progresiva.

Esta es la bibliografía consultada



CLINICS IN GERIATRIC MEDICINE

Clin Geriatr Med 24 (2008) 407–435

Diabetic Neuropathy in Older Adults

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Diabetic neuropathies (DN) encompass a wide range of nerve abnormalities and are common, with prevalence rates reported between 5% and 100%, depending on the diagnostic criteria [1–3]. DN affect both peripheral and autonomic nervous systems and cause considerable morbidity and mortality in both Type I and Type II diabetic patients. DN are the most common forms of neuropathy; they account for more hospitalizations than all other diabetic complications combined, and are responsible for 50% to 75% of nontraumatic amputations [4,5]. In older adults who have diabetes, peripheral neuropathies are especially troublesome because of their detrimental effects on stability, sensorimotor function, gait, and activities of daily living (ADL) [6–8]. In the United States for 1999 to 2000, 28% of adults aged 70 to 79 years and 35% of adults aged more than 80 years had peripheral neuropathy, based on a simple screen for reduced sensation at the foot [9]. In this article, the authors present and discuss the most recent approaches to the treatment of the common forms of diabetic neuropathy, including symmetric, focal, and diffuse neuropathies (Box 1) (Fig. 1). We also provide the reader with algorithms for recognition and management of common pain and entrapment syndromes, and a global approach to recognition of syndromes requiring specialized treatments based upon our improved understanding of their etiopathogenesis. A comprehensive

Portions of the text are from Witzke KA, Vinik AI. Diabetic neuropathy in older adults. Rev Endocr Metab Disord 2005;6(2):117–27; with permission.

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Endoneurial Capillary Abnormalities Presage Deterioration of Glucose Tolerance and Accompany Peripheral Neuropathy in Man

Soley Thrainsdottir,[1] Rayaz A. Malik,[2] Lars B. Dahlin,[3] Peter Wikstrand,[4] Karl F. Eriksson,[3] Ingmar Rosén,[5] Jesper Petersson,[1] Douglas A. Greene,[7] and Göran Sundkvist[4]

To explore whether microangiopathy is associated with disturbed glucose tolerance and peripheral neuropathy, we assessed endoneurial capillary morphology in sural nerve biopsies from men with diabetes, impaired glucose tolerance (IGT), and normal glucose tolerance (NGT). Baseline morphology was related to glucose tolerance and neuropathy at baseline and at follow-up 6 years later. Capillary density (in number per millimeters squared) at baseline was higher in subjects with diabetes ($n = 10$) compared with those with NGT ($n = 5$) at follow-up (median [interquartile range]) (86.0 [24.3] vs. 54.9 [17.1]; $P = 0.0200$) and in those progressing from IGT to diabetes ($n = 4$) compared with those with persistent IGT ($n = 4$) (86.7 [25.2] vs. 54.1 [14.6]; $P = 0.0635$). The capillary luminal area (in micrometers squared) was lower in subjects with NGT progressing to IGT ($n = 2$) or subjects with IGT progressing to diabetes ($n = 3$) compared with subjects with constant NGT ($n = 6$) or constant IGT ($n = 4$) (11.9 [2.4] vs. 20.8 [7.8]; $P = 0.0201$). The capillary basement membrane area (in micrometers squared) was increased in patients with peripheral neuropathy ($n = 10$) compared with those without ($n = 7$) (134.6 [68.8] vs. 75.5 [28.7]; $P = 0.0084$). In conclusion, increased capillary density was associated with current or future diabetes, decreased capillary luminal area with future deterioration in glucose tolerance, and increased basement membrane area with peripheral neuropathy. *Diabetes* 52:2615–2622, 2003

Peripheral neuropathy is common in diabetes, affecting ~50% of diabetic patients in the U.S. (1). Among 8,787 Italian diabetic patients attending outpatient clinics, the prevalence of clinical peripheral neuropathy was 32.8%, and this increased dramatically to 83.8% when quantitative neurological examination and nerve conduction studies were employed (2). Peripheral neuropathy is a leading and independent risk factor for mortality (3) and morbidity as a result of foot ulceration and amputation (4). Apart from improved glycemic control (5), there is no treatment for this condition.

Several recent studies (6–9) have demonstrated that subjects with impaired glucose tolerance (IGT) develop peripheral neuropathy. Indeed, in our recent study, subjects with IGT or type 2 diabetes and with peripheral neuropathy showed a comparable decrease in myelinated nerve fiber density (MNFD) (10). Both metabolic (11–14) and vascular (15–17) factors are important in the pathogenesis of peripheral neuropathy in diabetes. The exact relationship between the severity of hyperglycemia and these factors remains to be established. Diabetic patients without evidence of neuropathy demonstrate endoneurial microangiopathy. Microangiopathy may therefore precede the development of peripheral neuropathy (18). To clarify this issue, it is necessary to explore the relationship between glucose tolerance, peripheral neuropathy, and microvascular morphology.

Between 1975 and 1976, we initiated a prospective study in a population-based cohort of Swedish men aged 48 years who were defined as having diabetes, IGT, or normal glucose tolerance (NGT) after an oral glucose tolerance test (OGTT) (18). In this group, we previously reported an increase in skeletal muscle capillary density in subjects who progressed from IGT to diabetes (19). After 10–14 years from the start of this prospective study, we tested peripheral nerve function in representative subgroups (20) followed by sural nerve biopsy and assessment of the morphometry of myelinated nerve fibers in 30 subjects (10). Five to 6 years later, we reevaluated the subjects who previously underwent sural nerve biopsy with a new OGTT, measurements of plasma insulin concentrations, a neurological examination, neurophysiological tests, and a detailed evaluation of endoneurial capillary morphometry in their previously obtained baseline nerve biopsy. This study represents a unique opportunity to define the rela-

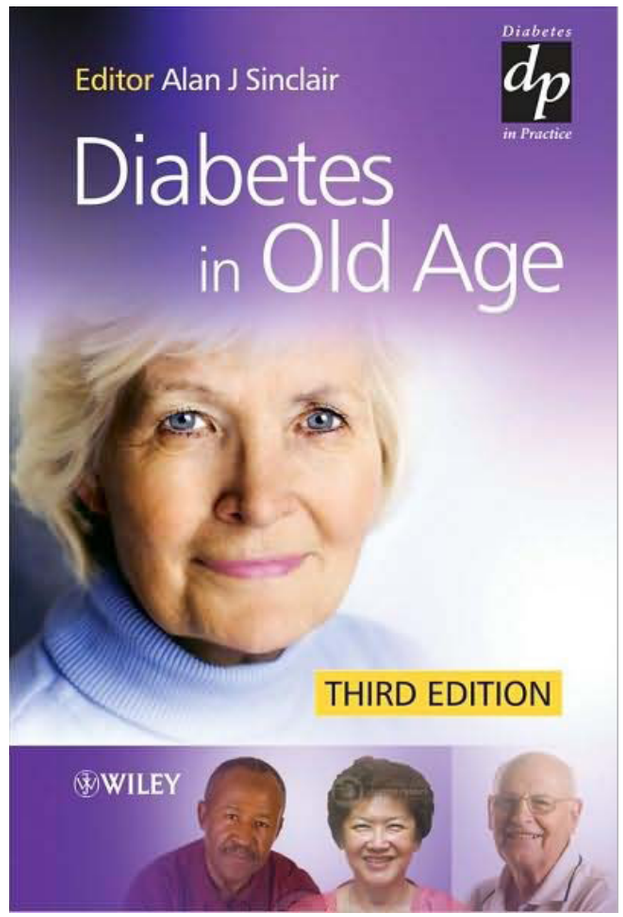
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IGT, impaired glucose tolerance; MNFD, myelinated nerve fiber density; NDI, Neuropathy Disability Score; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; SNAP, sural nerve action potential; SNCV, sural nerve conduction velocity.

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Entre otras….

Estrés oxidativo

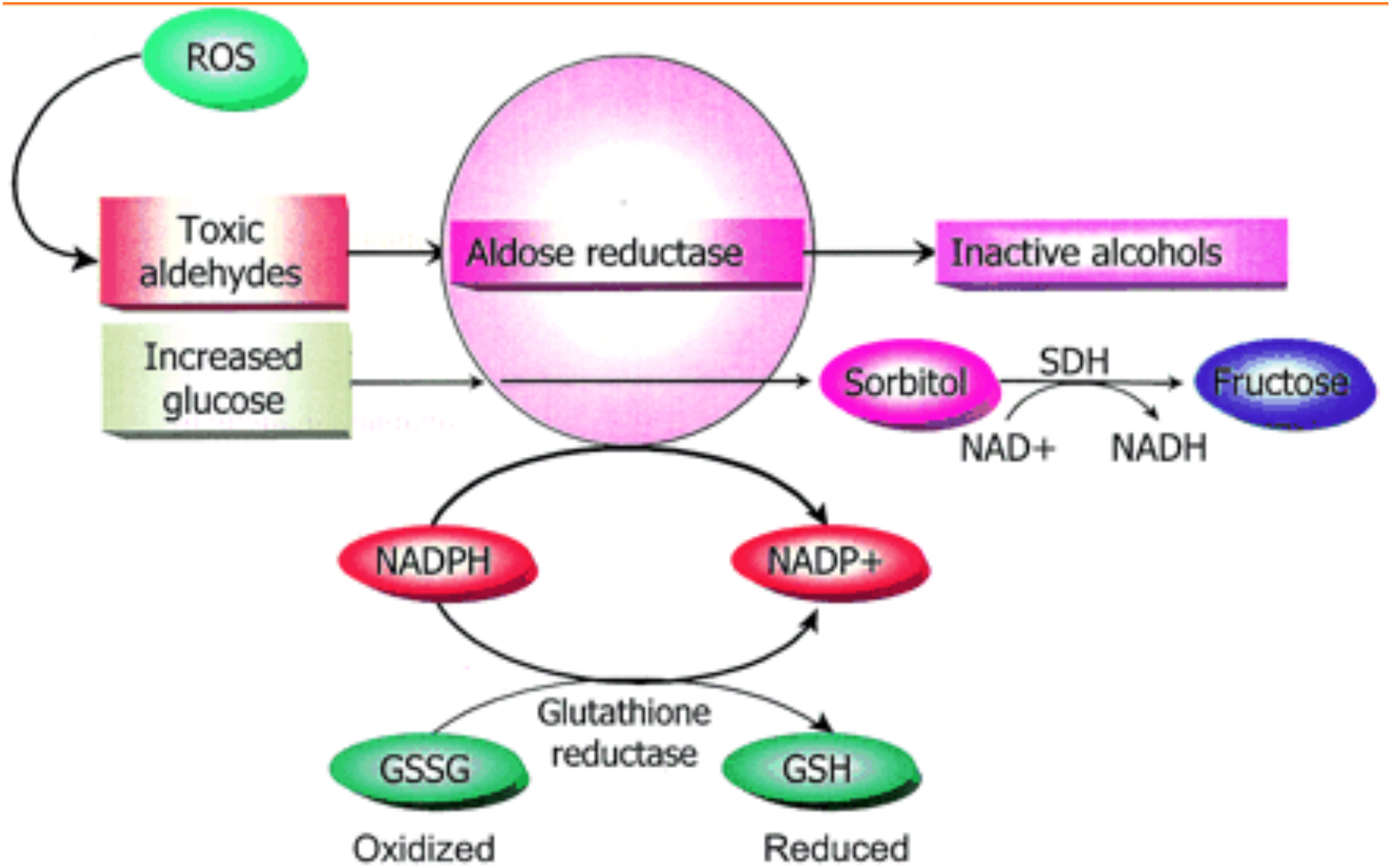
- Alteracion en la estructura y función de diferentes tejidos (DNA, proteinas y lípidos)

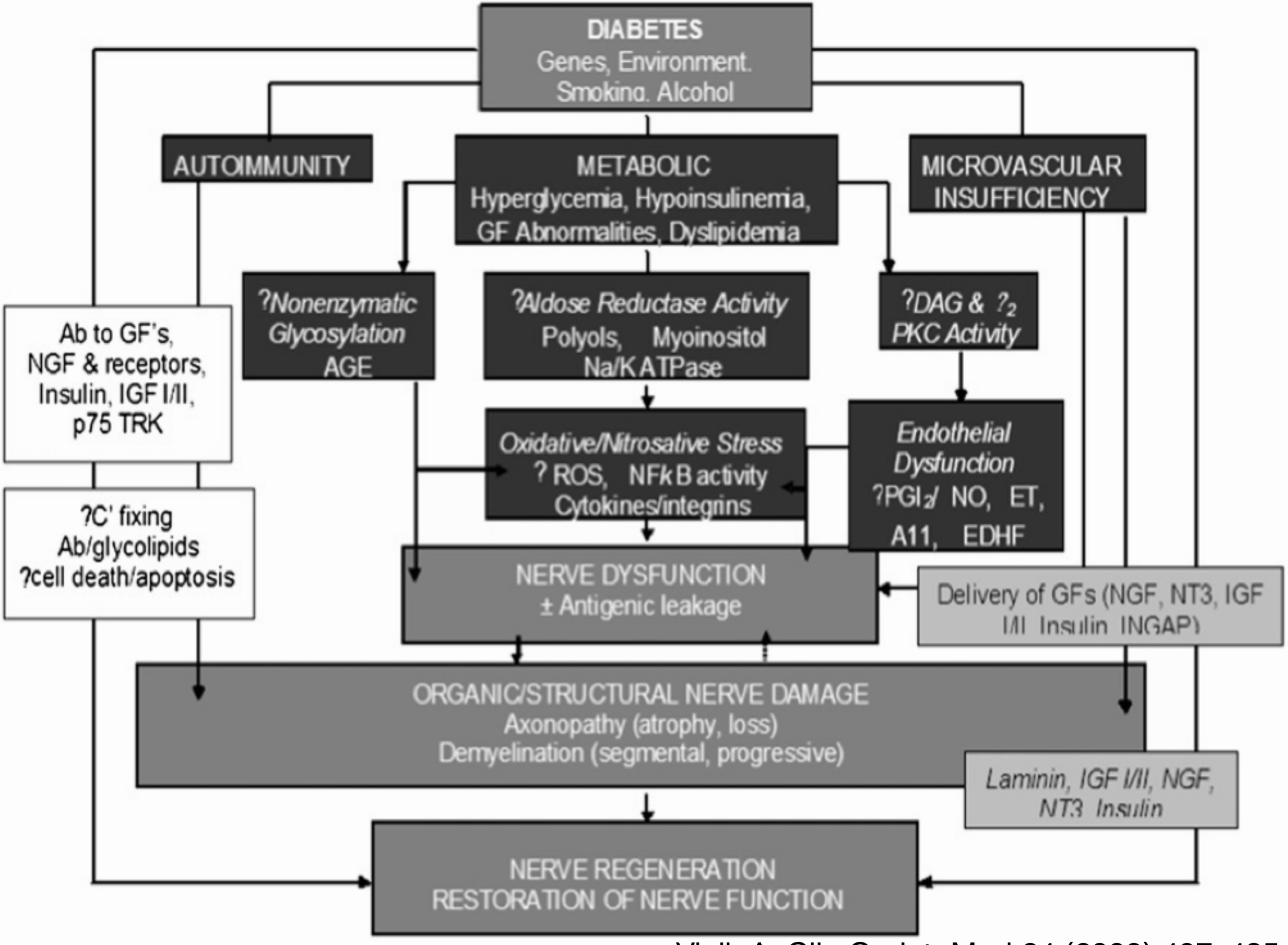
- Gatilla un serie de respuestas celulares:

- Activación de la PKC

- Activa el factor de transcripcion NF- B (transcription factor that itself activates many proinflammatory genes in the vasculature.)

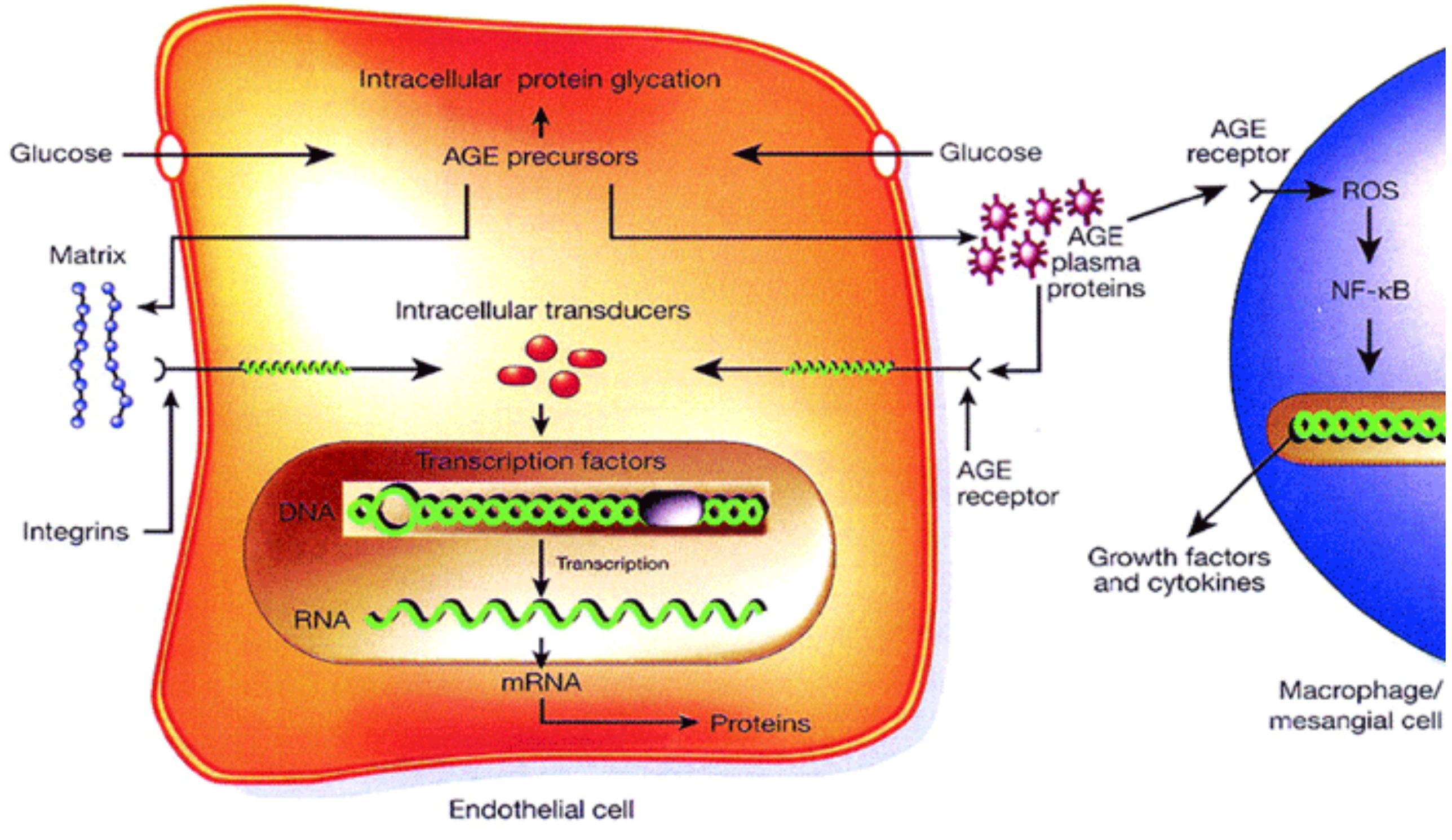
- Kinasas asociadas al estrés JNK

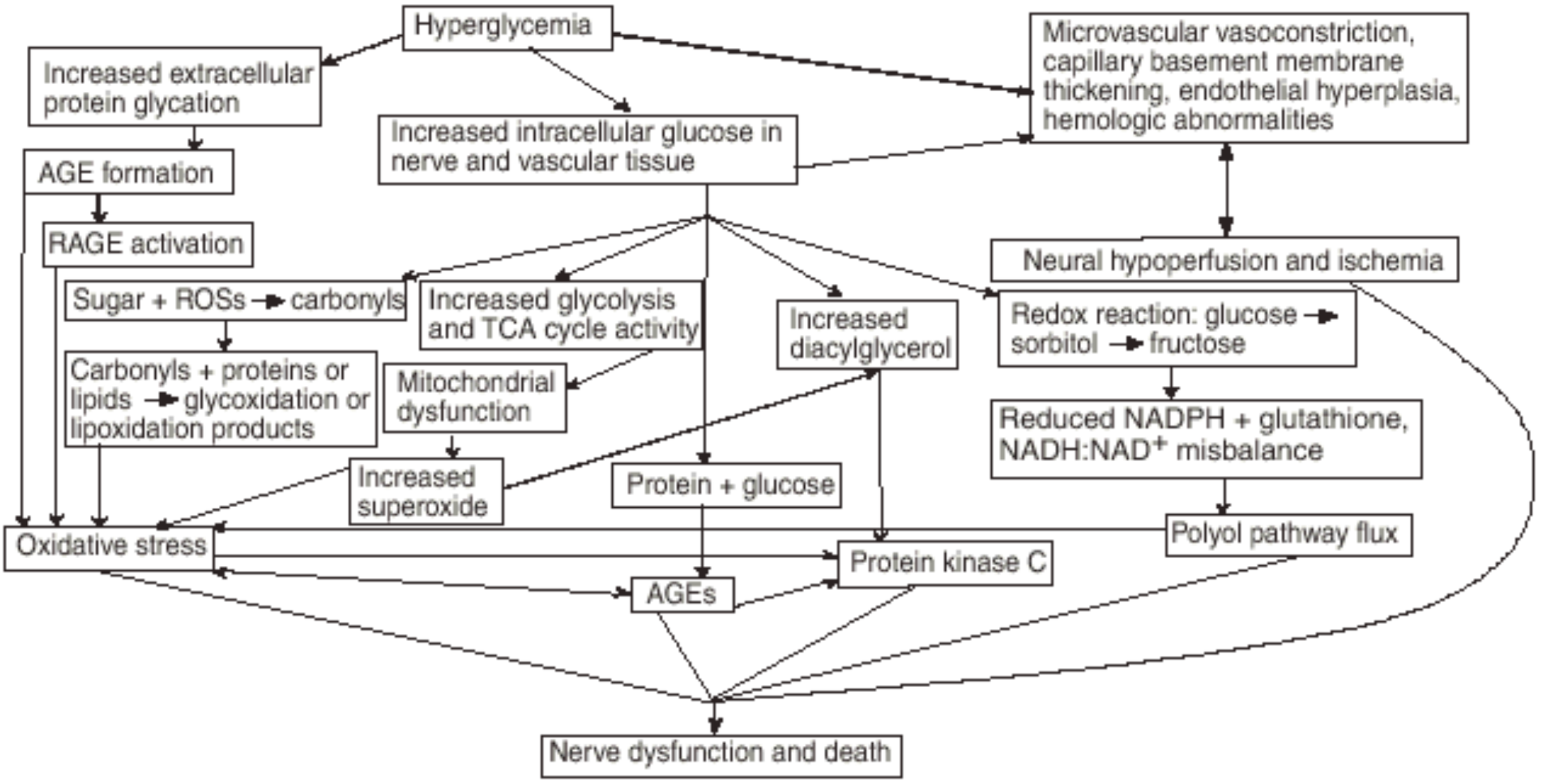

ROS
Toxic aldehydes
Increased glucose
Aldose reductase
Inactive alcohols
Sorbitol
SDH
Fructose
NAD+
NADH
NADPH
NADP+
Glutathione reductase
GSSG
GSH
Oxidized
Reduced



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AGF


Intracellular protein glycation
Glucose
AGE precursors
Glucose
AGE receptor
ROS
Matrix
AGE plasma proteins
NF-κB
Intracellular transducers
Transcription factors
DNA
Integrins
AGE receptor
Transcription
RNA
mRNA
Proteins
Growth factors and cytokines
Endothelial cell
Macrophage/ mesangial cell


Hyperglycemia
Increased extracellular protein glycation
AGE formation
RAGE activation
Sugar + ROSs → carbonyls
Carbonyls + proteins or lipids → glycoxidation or lipoxidation products
Increased intracellular glucose in nerve and vascular tissue
Increased glycolysis and TCA cycle activity
Mitochondrial dysfunction
Increased superoxide
Increased diacylglycerol
Protein + glucose
Microvascular vasoconstriction, capillary basement membrane thickening, endothelial hyperplasia, hemologic abnormalities
Neural hypoperfusion and ischemia
Redox reaction: glucose → sorbitol → fructose
Reduced NADPH + glutathione, NADH:NAD+ misbalance
Polyol pathway flux
Oxidative stress
Protein kinase C
AGEs
Nerve dysfunction and death