Diabetic Neuropathy

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Control of blood sugar

- Sugar (glucose) required for metabolism and energy
- Produced from digestion and breakdown of starches
- Blood glucose concentration controlled by insulin
- Insulin made in β-cells in Islets of Langerhans in the pancreas
- Insulin controls transfer of glucose from blood into many cells

Diabetes Mellitus

- Defect in the glucose control system
- Type 1 diabetes
  - ‘Juvenile onset diabetes’
  - ‘Insulin dependent diabetes (IDDM)’
  - Reduced insulin production
  - Caused by autoimmune destruction of insulin-producing cells
  - Treated with insulin replacement

Diabetes Mellitus

- Type 2 diabetes
  - ‘Late onset diabetes’
  - ‘Non-insulin dependent diabetes (NIDDM)’
  - Reduced sensitivity to insulin
  - Associated with obesity, physical inactivity, poor diet, genetic predisposition
  - May eventually become IDDM

Diabetes Mellitus

- Drug categories for type 2 diabetes
  - Insulin secretagogues
    - Enhance insulin secretion (eg Sulphonylurea)
  - Insulin sensitisers
    - Enhance muscle cell sensitivity (PPARg agonists)
    - Slow down glucose release from liver (Biguanides)
  - Digestion modulators
    - Hinder starch digestion (α-glucosidase inhibitors)
    - Block fat absorption to reduce obesity (Orlistat)

Long-term problems (1)

- Microvascular damage
  - Nephropathy (kidneys)
    - Damage to glomeruli
    - Blood albumin leaks into urine (diagnostic)
    - Loss of filtration capacity (kidney failure)
  - Retinopathy (eyes)
    - Proliferation of fragile blood vessels in retina
    - Blood protein leaks into eye
    - Scar tissue damages retina
  - Neuropathy (nerves)

Long-term problems (2)

- Macrovascular damage
  - Atherosclerosis (deposits in blood vessels)
    - 75% of early diabetic deaths
  - Angina (reduced blood flow to heart)
    - Chest pains
- Hypertension (high blood pressure)
  - Heart and kidney disease

‘Diabetes - a leading cause of death in USA’

Diabetic Neuropathy

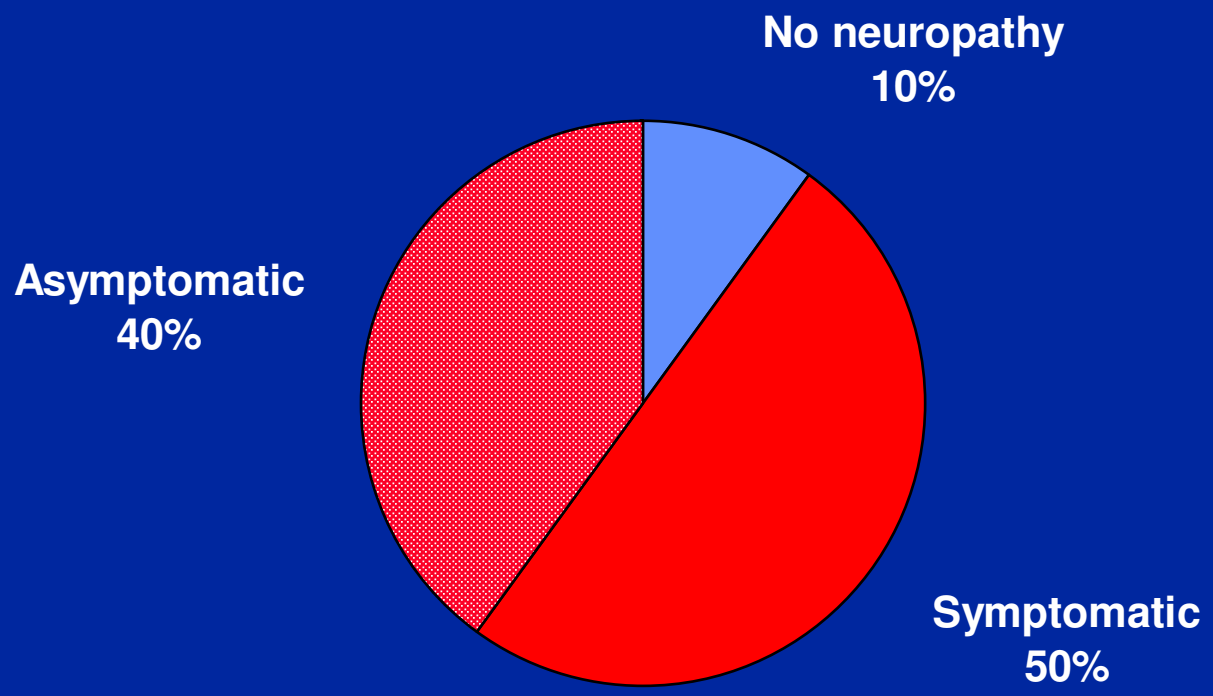
- Damage to nerve fibres and capillaries
- Symptoms depend on nerves involved
  - Motor fibres → Muscular weakness
  - Sensory fibres → Loss of sensation
    - also prickling, tingling, aching and pain
  - Autonomic fibres → loss of function
    - functions not under conscious control such as digestion, bladder, genitals, cardiovascular.

Diabetic Neuropathy

- Other Consequences
  - Diabetic foot (15% of all diabetics)
  - Compression neuropathies
    - eg carpal tunnel syndrome
- Risk factors
  - Smoking, >40 years old, poor glucose control
  - Affects Type 1 and Type 2

Incidence of Diabetic Neuropathy

as a proportion of all diabetics 20 years after diagnosis



Diabetic Neuropathy

- Current treatment
  - Careful blood sugar control
  - Drug treatment of symptoms
    - eg painkillers, metacloprimide, Viagra
  - Diet
  - Foot hygiene and maintenance
  - Exercise

Underlying Mechanisms

Agreement not yet reached on exact causal relationship between insulin imbalance and nerve damage.

The relative importance and inter-relationship of the various mechanisms is the subject of ongoing research and debate.

Physical manifestations

- Nerve fibres degenerate
- Blood vessels supplying the nerves are ‘grossly diseased’

Any theory needs to account for both

Pathways of action

- Polyol pathway
- Triose phosphate effects
- Failure of nerve growth & repair mechanism
- Fatty acid metabolism

Polyol Pathway

- Polyol = Polyhydroxy alcohols
- High blood glucose
  - Nerve cell and capillary membranes have insulin-independent glucose transport.
  - High intra-cellular glucose levels
  - Conversion of glucose to sorbitol in nerve cells by aldose reductase enzyme
  - Sorbitol cannot cross membranes and therefore accumulates

Polyol Pathway

- Consequences of high sorbitol concentration:
  - Osmotic damage to nerve cells
  - reduction in nerve myoinositol
  - Inhibition of nitric oxide (NO) production
    - Aldose reductase competes for NADPH
    - NO is vasodilator
  - Increased production of free radicals
    - Superoxide, hydrogen peroxide, hydroxyl
    - Formed during mitochondrial respiration
    - Increased oxidative stress (proteins, lipids, DNA)

Polyol Pathway

- Treatment possibilities
  - Aldose reductase inhibitors
  - Supplemental myoinositol
  - Nitric oxide stimulation/sensitisation
  - Vasodilators
  - Antioxidants

Triose phosphates

- High intracellular glucose leads increased production of triose phosphates
  - Activation of protein kinase C (PKC) via DAG
    - Damages capillaries (permeability, contractility)
    - Damages nerve function
  - Non-enzymic reaction with proteins & DNA
    - Advanced Glycation End-products (AGEs)
    - Damage to capillaries and nerve fibres
    - Specific cellular AGE receptors
    - Protein cross-linking

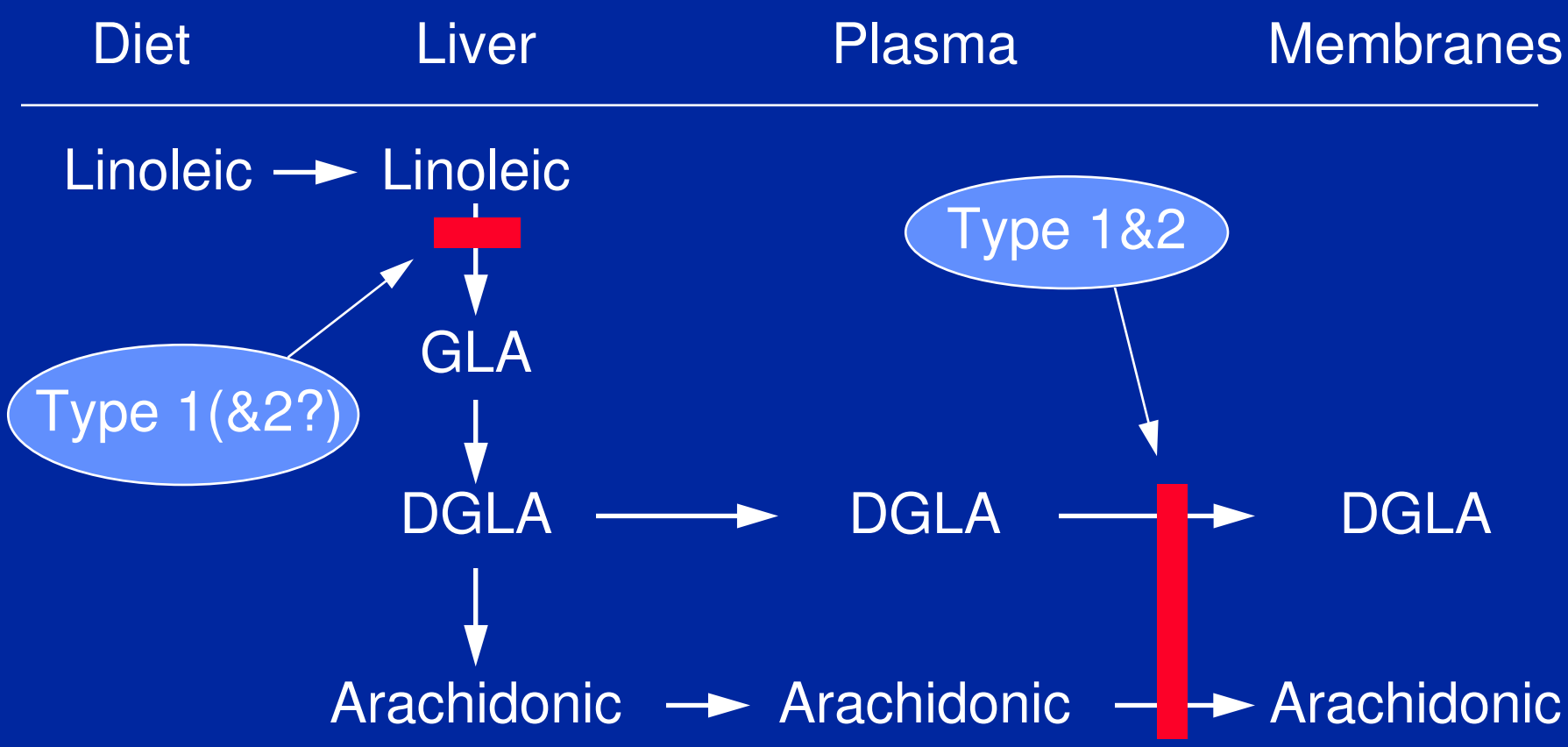
Treatment possibilities

- PKC inhibitors
- Remove AGE precursors
  - α-Oxoaldehyde scavengers
- Block AGE receptors
- Block protein cross linking
  - Aminoguanidine

Nerve Growth and Repair

- Reduced levels of :
  - Nerve Growth Factor (NGF)
  - Neurotrophin 3 (NT-3)
- Supplementation does not influence nerve blood flow or motor conduction velocity in rats

Fatty acid metabolism



Fatty acid metabolism

- Functions of DGLA and AA in nerves
  - Incorporated into membranes
    - required for normal nerve structure, which is required for normal nerve conduction
  - Required for regulation of nerve conduction
    - via inositol/calcium cycle and PGE_1
  - Required for microvascular system
    - DLMG - Prostaglandin E_1
    - AA - Prostacyclin

Fatty acid metabolism

- Failure of incorporation may be because of:
  - actual reduced incorporation; or
  - excessive peroxidation; or
  - excessive removal
- Overcome conversion blockage by supplementing with GLA
- Evening primrose oil contains 9% GLA

GLA Animal Studies

- All studies in streptozotocin rats show prevention and reversal of neuropathy
- Acts primarily through increased nerve blood flow
- Mainly through increased prostacyclin and hence nitric oxide
- No effect on polyol pathway

GLA Human Studies

- 12 x 500 mg capsules/day EPO
- 3 randomised placebo-controlled studies

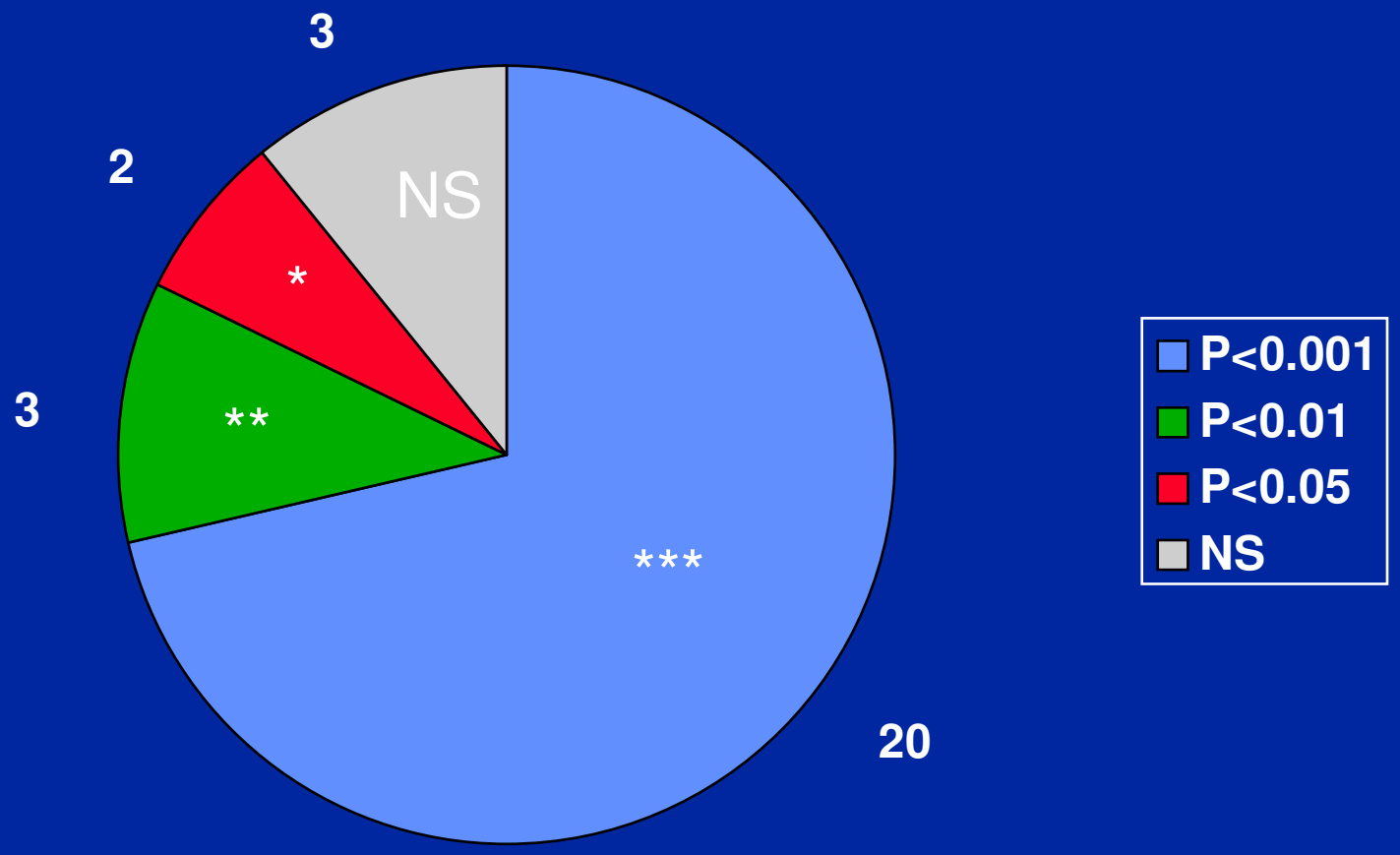
  1) 22 patients in 1 centre
     - All parameters improved in GLA group
     - All parameters deteriorated in placebo group
     - Many of differences statistically significant
  2) 111 patients in 7 centres
  3) 293 patients in 10 centres

GLA Human Studies

- 28 Parameters measured in studies 2&3:
  - Conduction velocity
  - Action potential amplitudes
  - Detection of temperature changes (hot & cold)
  - Sensory functions
  - Muscle strength
  - Reflexes

GLA Human Studies

Combined results (n=404)



28 parameters - all improved relative to placebo

GLA Human Studies

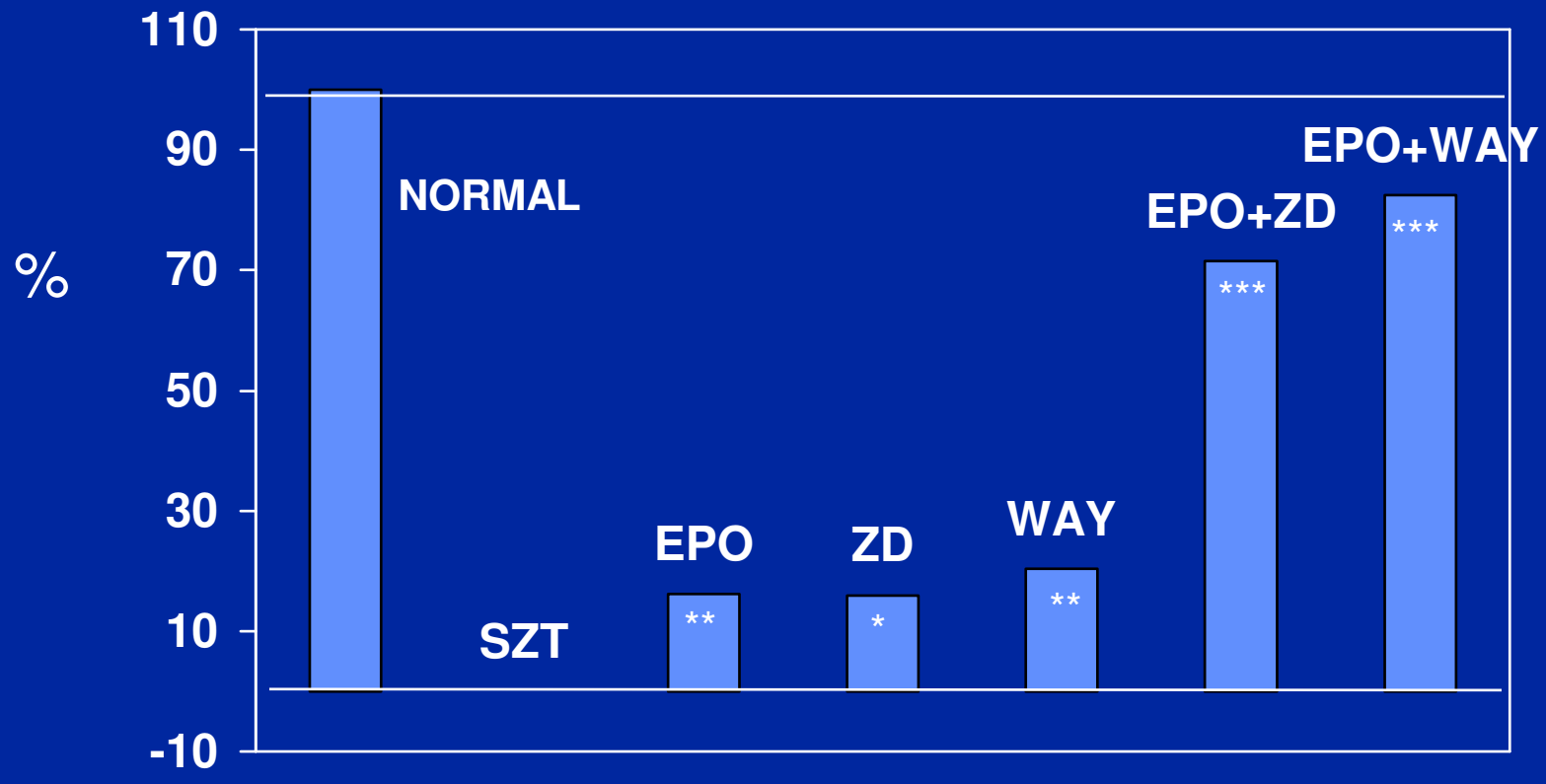
- Confirm animal studies
- Demonstrate beneficial effect
- No effect on glycosylated haemoglobin
- Very safe
  - 26 events reported on active (n=202)
  - 34 events reported on placebo (n=202)
  - mostly mild gastrointestinal upset
  - none serious

GLA + ARIs

- GLA does not affect polyol pathway
- Complimentary effect?
- Streptozotocin-treated rats
- Threshold doses of EPO and 2 ARIs
- Measure:
  - Nerve conduction velocity
  - Vascular conductance
- Use two ARIs with different modes

GLA + ARIs

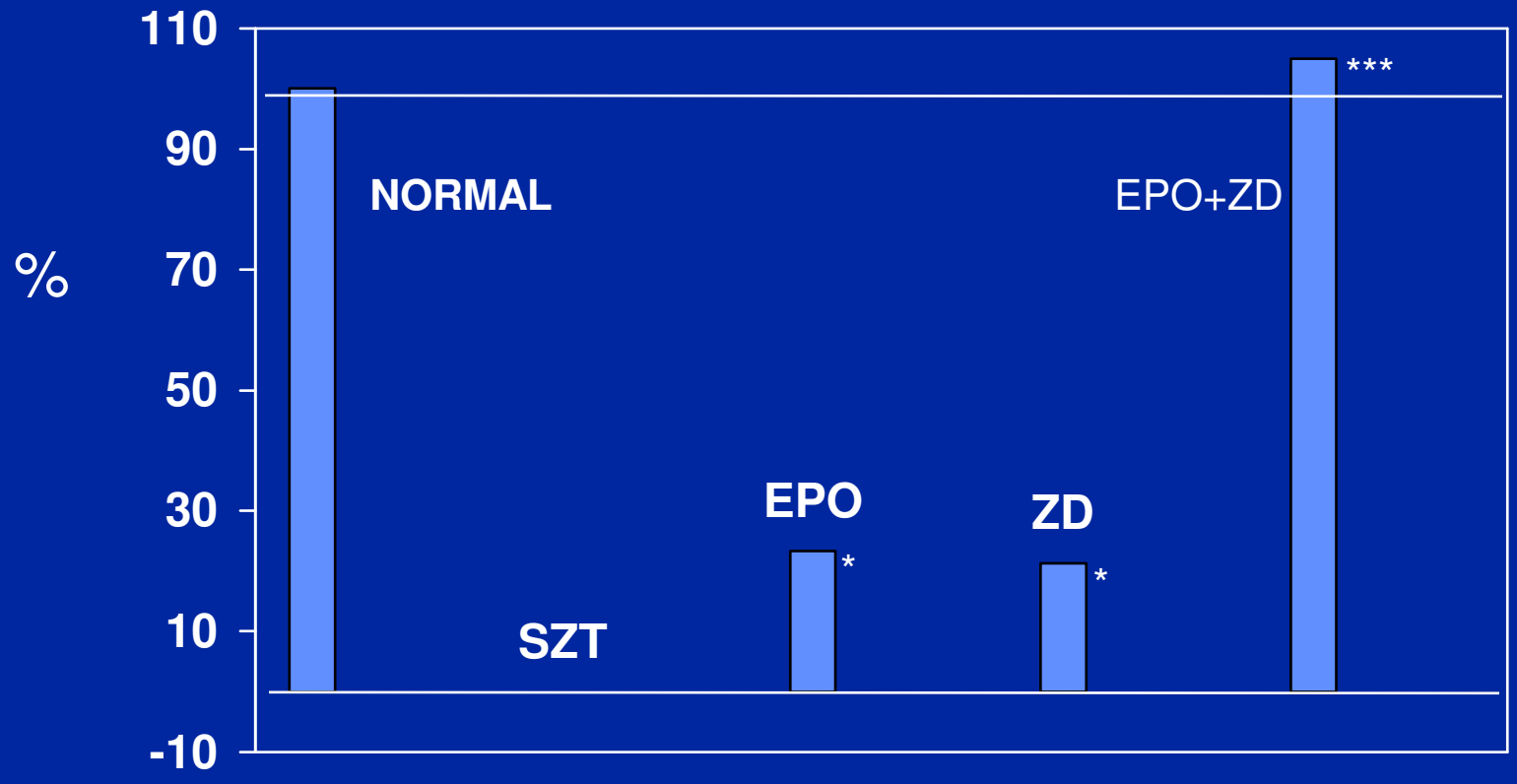
Effect on nerve conduction velocity



WAY = WAY121509 ZD = ZD5522

GLA + ARIs

Effect on nerve vascular conductance



ZD = ZD5522

GLA + ARIs

Combined effect is much greater than additive

Dose required to produce same effect as other component

	Additive	Observed
EPO required	0.8x	13.3x
ZD5522 required	1.8x	6.8x

GLA + ARIs

- No effect of EPO on polyol pathway
- No effect on glycosylated haemoglobin

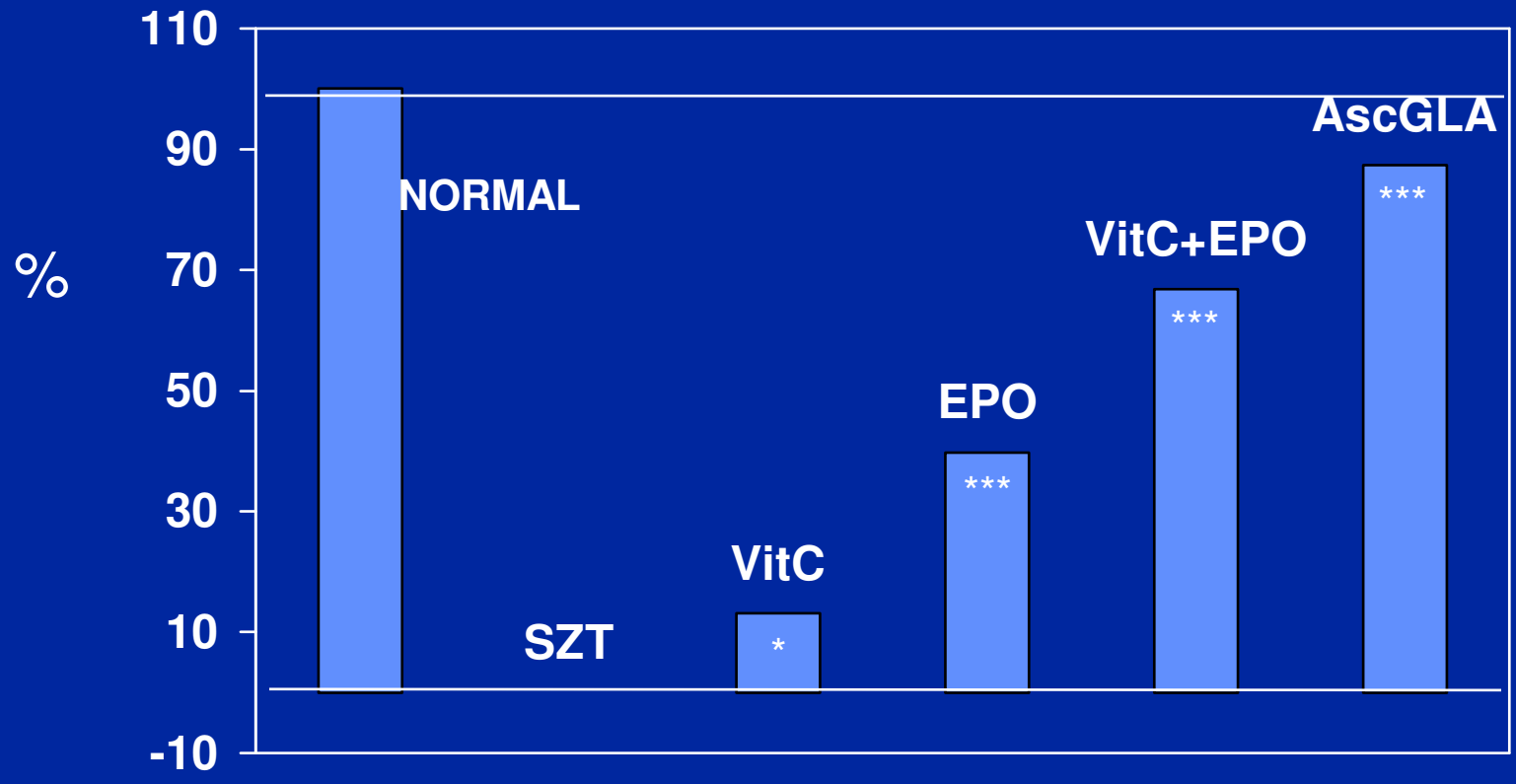
- Vitamin C as an alternative?
  - Effective ARI
  - Powerful antioxidant (protects GLA)
  - May be deficient in diabetics
  - Transport into cells also controlled by insulin

GLA + Vitamin C

- Streptozotocin-treated rats
- Included meglumine salt of ascorbyl-GLA
  - Novel compound
  - Delivers vit C and GLA to same site
  - GLA moiety makes vit C lipid soluble

GLA + Vitamin C

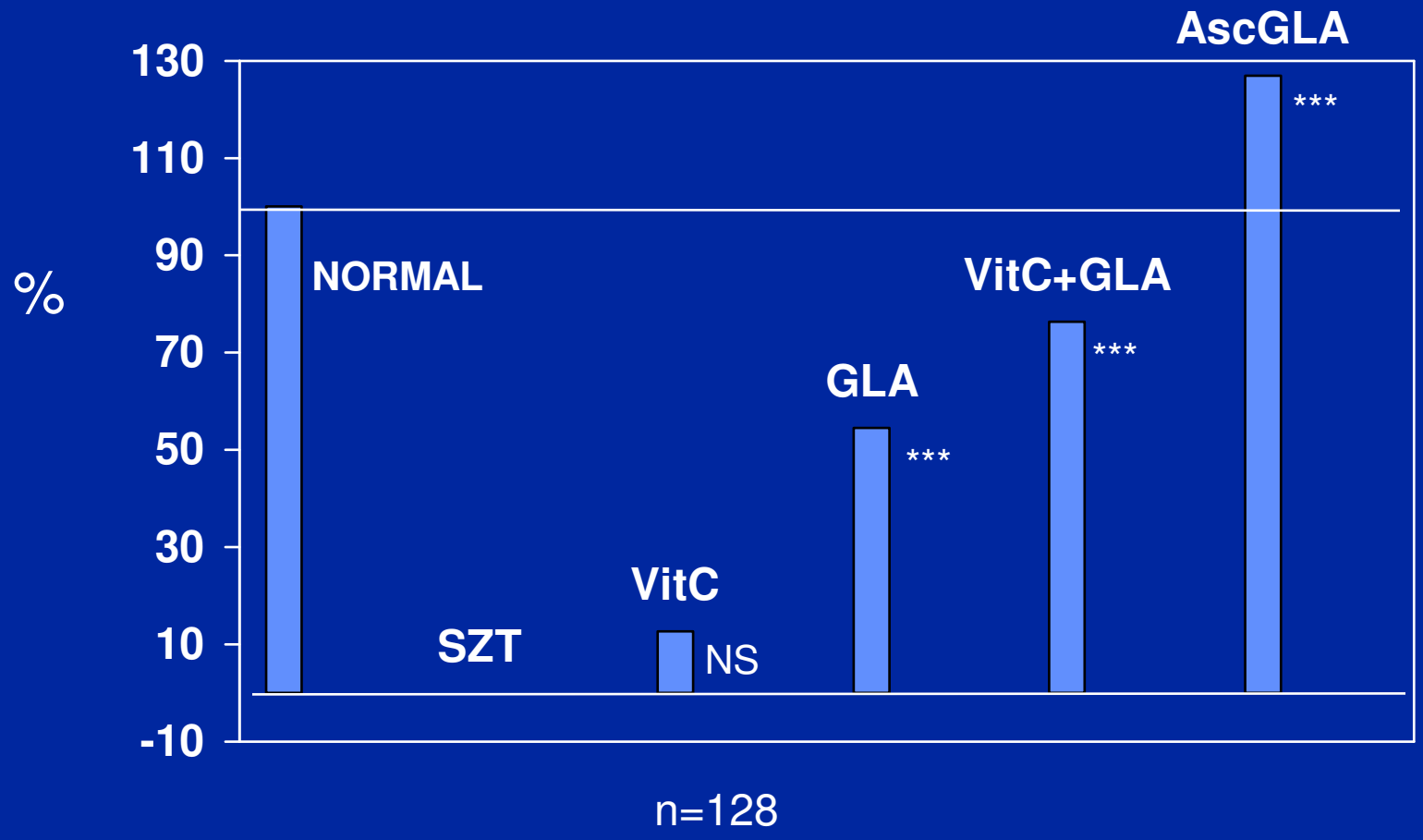
Effect on nerve conduction velocity



n=128

GLA + Vitamin C

Effect on nerve vascular conductance



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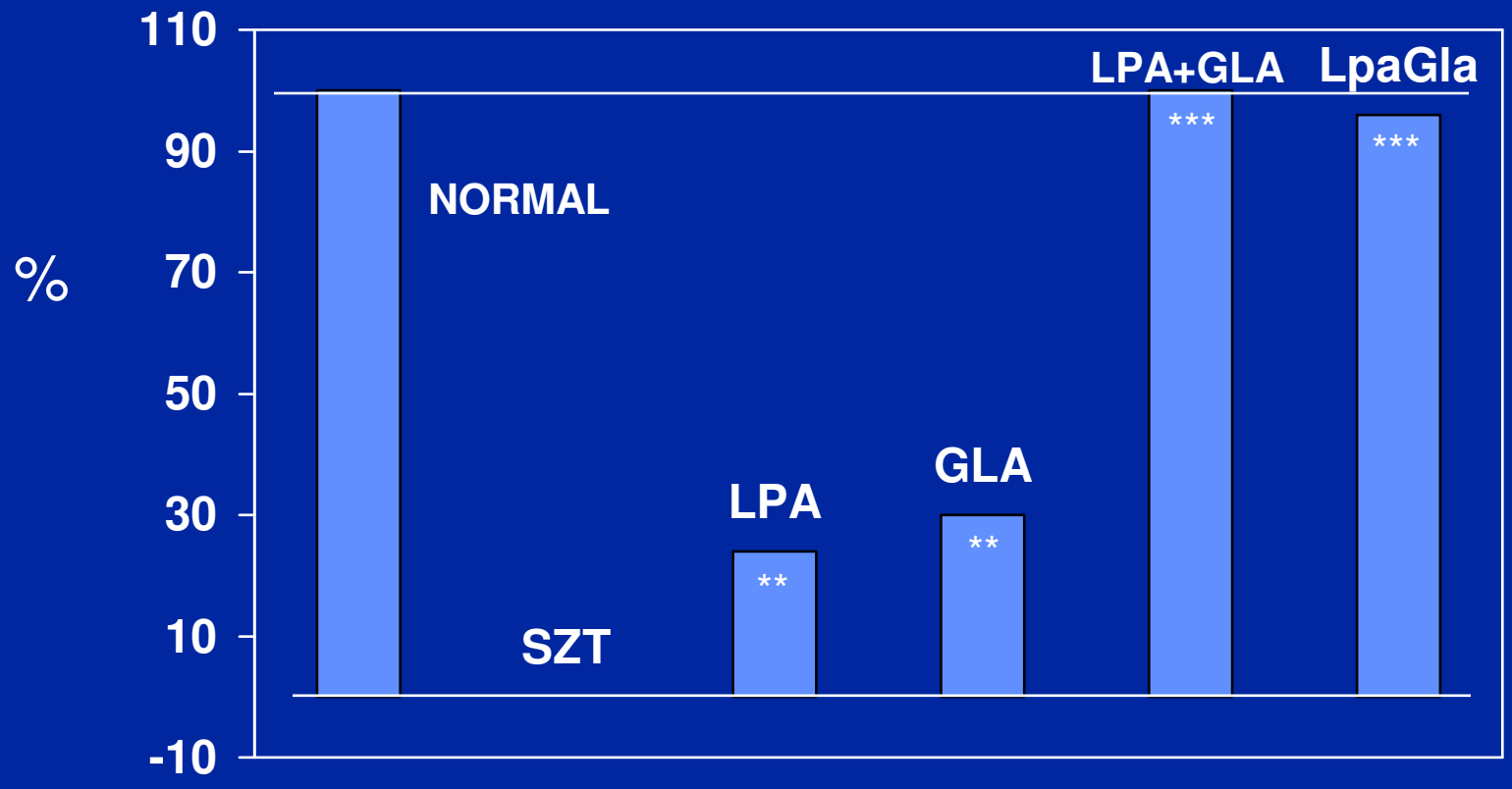
GLA + Lipoic acid

- Lipoic acid is a naturally occurring free radical scavenger
- ‘metabolic antioxidant’
- Regenerates major antioxidants
  - vit C, glutathione, thioredoxone, ubiquinone
- Protects NO synthesis

GLA + Lipoic Acid

Effect on nerve conduction velocity



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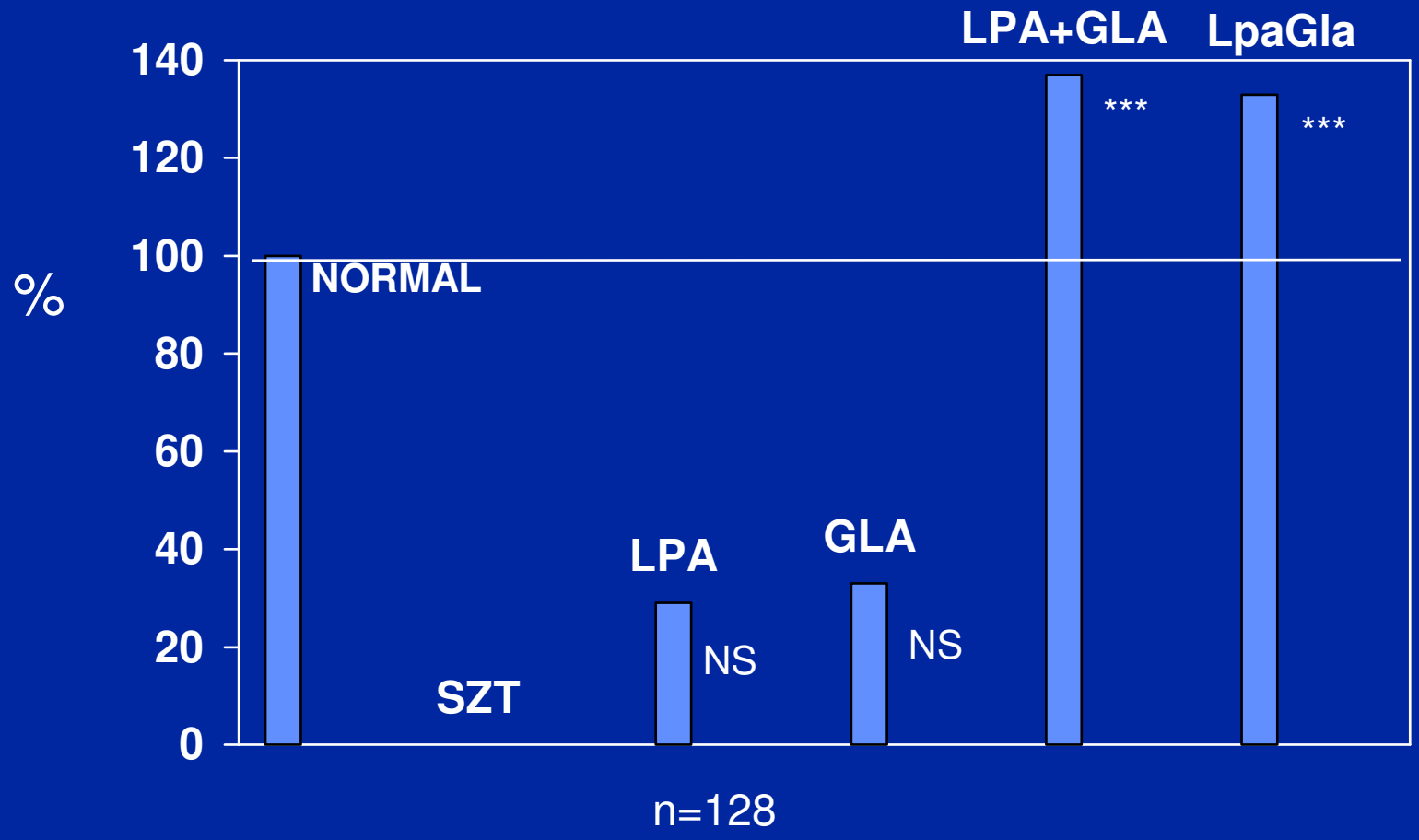
GLA + Lipoic Acid

Effect on nerve vascular conductance



Synergistic Effects

- GLA acts via prostacyclin
- Vitamin C and Lipoic Acid act via Nitric Oxide
- Together their effect is much greater than would be expected from additivity
- Potential treatment for neuropathy?

Commercial Situation

- EPO was rejected by regulators
- GLA therefore discredited in industry
- Original company folded
- Patent protection running out
- May not see products commercialised