ANIMAL MODELS AND GENE THERAPY FOR DIABETIC NEUROPATHY

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Introduction: Diabetic Neuropathy

• Neural dysfunction characterized for lower nerve signal conduction speed, axonal degeneration and strange regeneration of axons. This neuropathy leads to different abnormalities like numbness, tingling, burning, and shooting pain in the legs and reduced pain, touch, and vibratory perception in a symmetrical stocking glove distribution

• Most common complication in diabetes, appears in more than 50% of patients

• It develops because the hyperglycemia but its specific pathways are still in study (Figure 1)

• No available treatment for diabetic neuropathy other than glycemic control and diligent foot care

• For these reasons:

1. It is important to have animal models for diabetes to study its complications
2. It is necessary develops new therapies for diabetic neuropathy

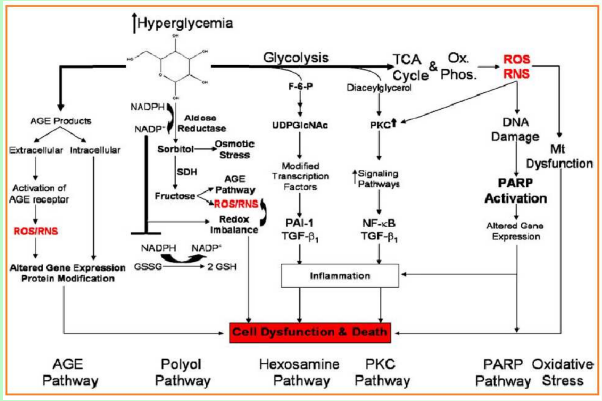

Figure 1. Diagram of hyperglycemic effects on biochemical pathways in diabetic neuropathy. Modified from Figueroa-Romero C, Sadidi M, Feldman EL. Mechanisms of disease: the oxidative stress theory of diabetic neuropathy Rev Endocr Metab Disord 2008 Dec;9(4):301-314

Objectives

• Study different animal models for reproduce diabetes type I and their characteristics

• Find the newest gene therapies to treat diabetic neuropathy and the clinical trials done until now

Methods

Analyze different kind of information sources like:
- Research papers
- Webs of diabetic associations
- Webs of clinical trials

Choose the best information and data to achieve the previous objectives

Animal Models for Diabetes Type I

Classification	Model	Characteristics	Advantages	Disadvantages
Chemically induced models	Drug: STZ	Necrosis of pancreatic β-cells by: Alkylation of DNA and production of ROS	Easy administration, cheap and good experimental protocols for many species	Toxicity in other parts of the body: renal failure and endothelial inflammation/dysfunction Without autoimmunity
	Drug: Alloxan	Destruction of pancreatic β-cells by: Superoxide radicals and massive increase of cytosolic calcium concentration	Easy administration and cheap	Range of diabetogenic dose is quite narrow High loss of animal from kidney tubular cell necrotic toxicity Without autoimmunity
Surgical models	Pancreatectomy	Partial or complete removal of the pancreas First model used in investigation	–	Expensive, high loss of animals and not autoimmunity
Animal strains that spontaneously develop diabetes type I	NOD mouse	Diabetes: 24-30 weeks Autoantibodies: insulin, GAD and IA-2 Hiperglycaemia, glycosuria, polydipsia, polyuria, thyroiditis and Sjögren's syndrome	Autoantibodies and clinical signs equal to humans Animal model to study autoimmunity in diabetes	Insulitis has many differences from human insulitis Resistance to ketoacidosis
	BB rat	Diabetes: 8-16 weeks Autoantibodies: pancreatic islets and GAD Hiperglycaemia, insulinopaenia, polyuria, polydipsia, ketoacidosis and lymphopenia	Development of the illness similar to humans (without peri-insulitis) All the clinical features seen in humans	They have T-cell lymphopenia: T $CD8^+$ are missing and T $CD4^+$ are greatly reduced
	LETL-KDP rat	Diabetes: 8-16 weeks Hiperglycaemia, insulinopaenia, polyuria, polydipsia, ketoacidosis Lymphocyte infiltration in thyroid an kidney	All the clinical features seen in humans Not lymphopenic High percentatge of animals with the disease (70-80%)	They exhibits lymphocyte infiltration in thyroid and kidney
	LEW-iddm rat	Newest model Diabetes: 60 days Low blood levels of insulin, hyperglycaemia, glycosuria and ketonuria	Not lymphopenic High percentatge of animals with the disease (70%) Without lymphocyte infiltration in other organs different to pancreas	Without autoantibodies against GAD and IA-2 Residual levels of insulin in blood

Table 1. Different animals models for diabetis type I with their characteristics. STZ:streptozotocin, NOD:non-obese diabetic, ROS: reactive oxygen species, *GAD:glutamic acid descarboxilasa, IA-2:tyrosine phosphatase ICA512, BB:biobreeding, LETL long evans Tokushima lean and LEW-iddm: Lewis insulin-dependent diabetes mellitus.*

Gene Therapy for Diabetic Neuropathy

• Gen therapy: introduction of genetic material into cells using viral or non-viral vectors that induces expression or repression of some genes or proteins

• Strategy to treat diabetic neuropathy: express some factors or proteins that show neuroprotective effects for reverse or avoid damage in patient's neurons

• Many proteins show neuroprotective effects in vitro and in animals models but only 3 proteins have been used in human clinical trials:

- ❑ VEGF (Vascular Endothelial Growth Factor)
- ❑ NGF (Nerve Growth Factor)
- ❑ GAD 67 (Glutamic Acid Decarboxylase)

• The actual results of these clinical trials (Figure 2), don't show enough effectiveness .

• New factors are in study and they show promising results in mice model:

- ❑ EPO (Erythropoietin)
- ❑ SOD + MTs (Super Oxide Dismutase + Metallothionein)

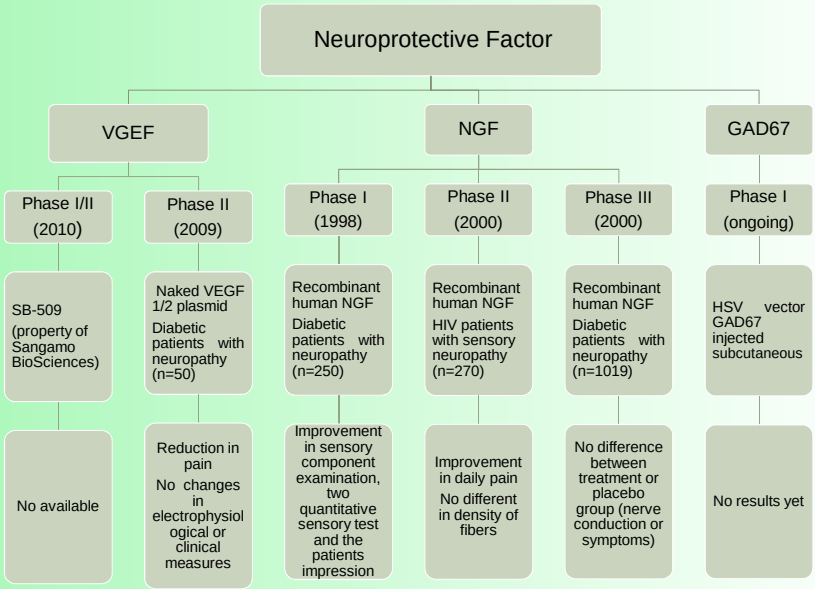

Figure 2. Representation of the characteristics and results of different clinical trials for treatment of DN. In this order we can see: factor, phase of clinical trail, treatment and results.

Conclusions

- ➢ Pathways to develop DN are still in study
- ➢ Many animal models for diabetes type I exits and everyone of them has its characteristics and limitations
- ➢ The most used for study diabetic complications: mouse injected with STZ (easy and cheap)
- ➢ Gene therapy is a new approach to treat DN but only 3 kind of proteins were used in clinical trails until now (VEGF, NGF, GAD 67) with poor results
- ➢ New proteins and factors are in study to future and necessary clinical trials to treat diabetic neuropathy