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EXCEL Medical Bulletin

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CILNIBLU (CILNIDIPINE) IN NEUROPATHIC PAIN

Diabetic neuropathic pain is one of the most common chronic complications of diabetes and one of the most common types of neuropathic pain to be treated. It is a type of chronic pain with a morbidity rate that is increasing annually, is associated with severe and long-lasting clinical symptoms that seriously affect patient quality of life.

Diabetic neuropathy is a common complication affecting almost 50% of the diabetic patients. In India, various studies report a prevalence of diabetic neuropathy ranging from 18% to 51% making it a burden on the health industry in India.

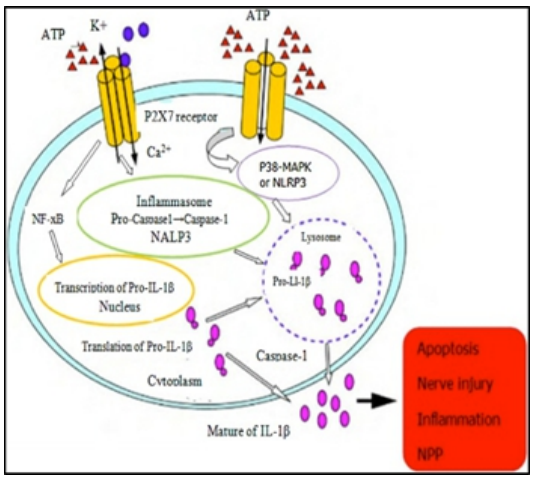
TRANSMISSION OF NEUROPATHIC PAIN

The microglial cells that are a specialized population of macrophages found in the central nervous system play a crucial role in neuroinflammation. Under pathological conditions the microglial cells undergo a process called ***microgliosis*** and upregulate the synthesis of a number of substances such as cytokines which ultimately lead to neurodegeneration.

The purinergic 2X7 receptor (P2X7R) is an ATP gated non-selective cation channel involved in the transmission of pain information. The P2X7Rs are widely distributed and functional at the innate immunity cells like the lymphocytes, granulocytes, macrophages, dendritic cells as well as the microglial cells.

ACTIVATION OF P2X7Rs

The injured neurons trigger the ATP release and thereby activate P2X7Rs on adjacent glial cells to release ATP in an autocrine manner. Through this cascade reaction, the ATP signal is amplified and promotes the formation of plasma membrane pores and release of cytokines such as IL-1β, plasminogen and TNF-β, which further activate glial cells and aggravate neuronal damage.



IL-1β is a major proinflammatory cytokine released by the activated macrophages in the microglial cells. This release of IL-1β from immunological cells is dependent on the activity of the P2X7Rs.

An efflux of K+ and influx of Ca+2 via the stimulation of P2X7Rs potentially activate the NLRP3 inflammasome which causes the activation of caspase-1, leading to the conversion of pro IL-1β to mature IL-1β. Thus, the P2X7R is involved in the pathogenesis of inflammation and neuropathic pain.

ROLE OF CILNIDIPINE IN ALLEVIATING NEUROPATHIC PAIN

Cilnidipine, a Ca+2 blocker, have been shown to inhibit P2X7Rs and microglial 1L-β release in recent preclinical studies. Another mechanism that has been hypothesized is its action on dynamin related protein-1 (DRP-1) a factor controlling the mitochondrial dynamics. An imbalance in the mitochondrial dynamics has been implicated in the activation of NLRP3 inflammasome resulting in the release of proinflammatory cytokines like IL-1β.

CILNIDIPINE: A PROMISING TREATMENT OPTION FOR DIABETIC NEUROPATHIC PAIN

The coexistence of raised blood pressure (BP) in people with type 2 diabetes mellitus (T2DM) is a major contributor to the development and progression of both macrovascular and microvascular complications. In patients with diabetes, it can triple the risk of coronary artery disease (CAD), double the total mortality and stroke risk, and can be responsible for up to 75% of all CVD events.

Thus, the use of cilnidipine as an anti-hypertensive in patients with type 2 diabetes with diabetic neuropathy would help alleviate the neuropathic pain and this newly identified pharmacological effect of cilnidipine could be effective for treating neuropathic pain.

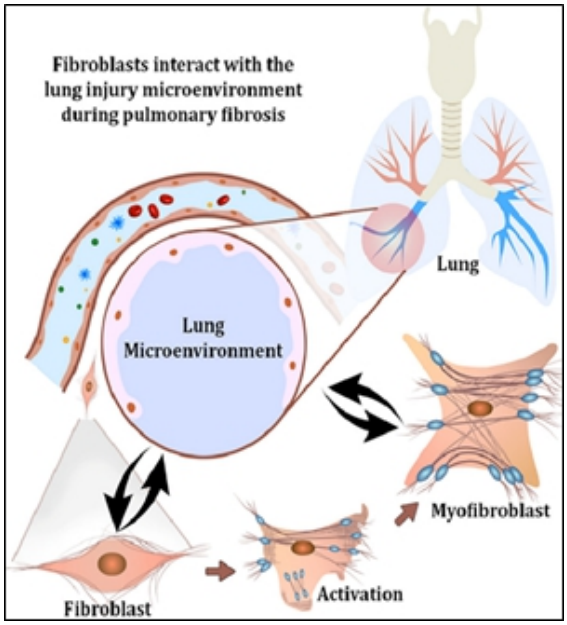
Source: Yamashita T et al. Cells 2021; 10(2): 434, Monif M et al. J of Neuroinflammation 2016; 13(173), Ren W et al. Int J of Mol Sci 2022; 23: 232, Wang A et al. Front Mol Neurosci 2021; 14(663649); Sangeetha RK & Suresh V. J of Fam Med & Primary Care 2022; 11(1): 113-117.

K-MET (METFORMIN) IN IDIOPATHIC PULMONARY FIBROSIS (IPF)

IPF is a chronic progressive interstitial lung disease with high morbidity, mortality, and limited treatment options. Type 2 diabetes is a common health condition that is present in many patients with IPF and is also thought to be a risk factor in the development of IPF.

Several environmental and microbial exposures play a role in IPF pathophysiology. The development of IPF occurs in the following steps:

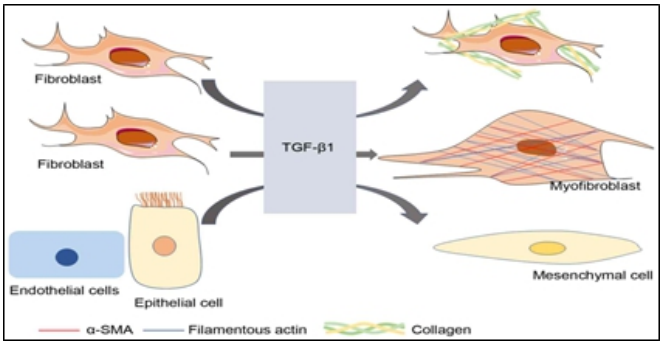
- ***Alveolar epithelial damage:*** The repeated micro-injury of the alveolar epithelium has been recognized as the first driver of an altered repair process where several lung cells develop aberrant behaviours, leading to the development and sustainment of the fibrotic process.
- ***Differentiation of the lung fibroblasts into myofibroblasts:*** This is the key step in the development of tissue fibrosis. The myofibroblasts express a protein called α smooth muscle actin (Asthma) as a marker of activated fibroblasts and are capable of extracellular matrix (ECM) production including collagen, laminin and fibronectin.



ROLE OF TRANSFORMING GROWTH FACTOR (TGF-) IN THE DEVELOPMENT OF IPF

- TGF-β is the most potent factor for the induction of myofibroblast differentiation. TGF-β1 regulates the terminal differentiation of the human lung fibroblast and promotes the synthesis of fibroblast extracellular matrix. The major sources of the TGF-β in the lungs are the alveolar macrophages and metaplastic type II alveolar epithelial cells. The activation of fibroblasts in response to TGF-β results in increased cell and nuclear size, enhanced protein synthesis capacity, enhanced ECM protein expression and additional metabolic and gene expression changes. The TGF- β family signals are conveyed through specific cell surface receptors to the intracellular mediators called Smads. The activation of the TGF-β1-Smad2/3 cascade plays an essential role in gene expression causing their phosphorylation & translocation from the cytoplasm to the nucleus where they function to control the gene expression. The upregulated ECM proteins expressed by the activated fibroblasts increases the collagen production; a hallmark of fibrosis.
- In addition to the ECM components, TGF-β induces integrins, matrix metalloproteases (MMPs), protease inhibitors and regulators of small GTPases (Guanosine triphosphate) which all participate in tissue remodelling and influence cell-ECM interactions.
- Apart from this, TGF-β is thought to promote lung fibrosis by suppressing the production of anti-fibrotic molecules such as hepatocyte growth factor and PGE2.
- TGF-β also inhibits the alveolar epithelial cell growth and repair.

Thus TGF-b is known to be a key player in the fibrotic processes acting on both fibroblasts and the alveolar epithelial cells.



1. Kinaan M, et al. Med Princ Pract 2015; 24: 401–415.

BENEFIT OF METFORMIN IN IPF

Many therapies have been investigated as potential treatment options for IPF, but most have been ineffective and, in some cases, harmful.

Currently, only two medications are approved by the U.S. FDA for IPF: the anti-fibrotic agents nintedanib and pirfenidone both demonstrating a slowed decline in lung function in patients with IPF. Subsequent pooled analyses and observational studies have suggested that their use reduces the risk of hospitalizations and improves mortality. Yet, only between 25% and 60% of patients with IPF are prescribed these anti-fibrotic medications may be due to high costs, side effects, uncertainty regarding IPF diagnosis, andtreatment deferral for presumed stable disease. Thus, additional therapies are needed to improve the health outcomes and reduce the risk of death among patients with IPF.

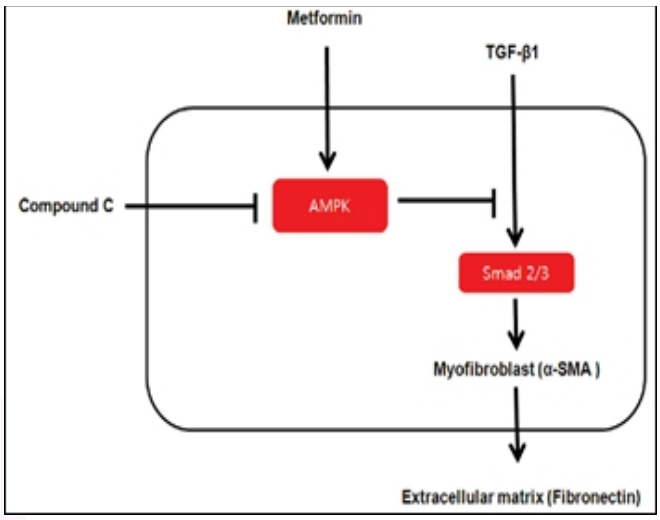
Metformin which is a potent AMPK activator, which is implicated in the glucose uptake in the skeletal muscle, is the first-line glucose-lowering medication in the management of T2DM. In addition to metformin's anti-glycaemic control, there is accumulating evidence demonstrating anti-neoplastic, anti-aging, and anti-fibrotic properties.

ANTI-FIBROTIC EFFECT OF METFORMIN

Metformin mainly exerts anti-fibrotic effects by affecting the TGF-β signalling pathway, cell metabolism, and oxidative stress. It inhibits the TGF-β1 production and decreases the phosphorylation & nuclear translocation of Smad 2/3.

Also, the decreased reactive oxygen species (ROS) generation induced by metformin treatment modulates TGF-β1-induced Smad2/3 phosphorylation and myofibroblast differentiation.

Moreover, metformin has also been shown to directly interact with TGF-β1 at its receptor-binding domain, thus suppressing the binding of TGF-β1 to its receptor and resulting in decreased activity.



According to the first real world study assessing the clinical benefits of metformin in T2DM patients with IPF showed that metformin therapy may be associated with improved clinical outcomes with respect to a significant reduction in all-cause mortality and risk of hospitalizations.

Source: Teague TT et al. Resp Res 2022; 23(9), Spagnolo P et al. European Resp J 2017; 50(PA859), Ye Z & Hu Y. Int J Mol Med 2021; 48(1): 132, WuM et al. J of Diab Res 2021; 6673525: 1-11.

PROTECTIVE EFFECT OF LEVOSULPIRIDE IN DIABETIC RETINOPATHY

Diabetic retinopathy and diabetic macular edema are microvascular diseases and a major cause of vision loss in adults. Current treatments like laser photocoagulation, intravitreal injections and vitrectomy are invasive and not always effective and most importantly temporary, emphasizing the need for additional therapeutic options.

Abnormal angiogenesis underlies multiple diseases including vasoproliferative retinopathies are characterized by excessive or insufficient proliferation of blood vessels.

VASOINHIBIN

Vasoinhibin is a proteolytically generated fragment of the pituitary hormone, prolactin (PRL) that inhibits the proliferation, migration, survival and permeability of the endothelial cells.

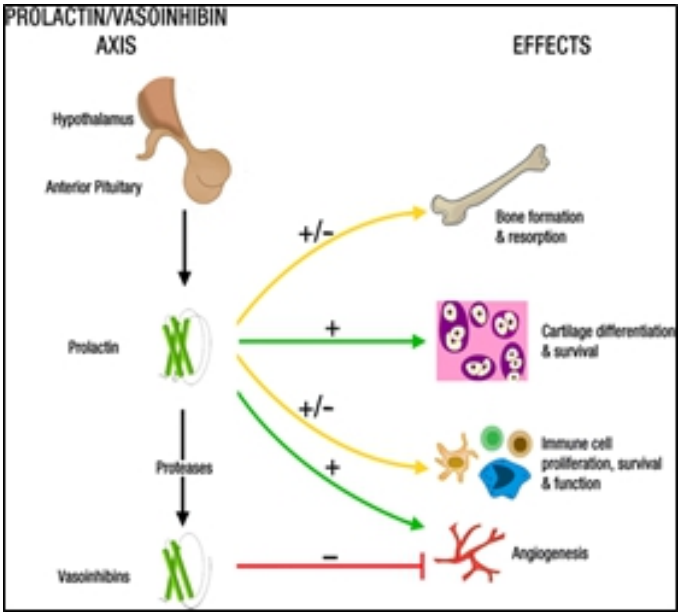
It is generated in the hypothalamus, pituitary and target tissues defining the PRL/vasoinhibin axis. The disruption of this axis can contribute to the progression of diabetic retinopathy, cardiomyopathy, pre-eclampsia and rheumatoid arthritis.

PRL/VASOINHIBIN AXIS

PRL stimulates blood vessel growth (angiogenesis), but acquires anti-angiogenic properties upon its cleavage to vasoinhibin.

The PRL/Vasoinhibin axis defines an endocrine system in which the pituitary secretion of PRL and proteases and thereafter conversion to vasoinhibin act in concert to regulate blood vessel growth and function, secretion of other hormones, inflammatory and immune processes, coagulation and behaviour.

The core element of the PRL/vasoinhibin axis is the generation of vasoinhibins which consists of the proteolytic cleavage of their precursor molecule, PRL and make it anti-angiogenic.

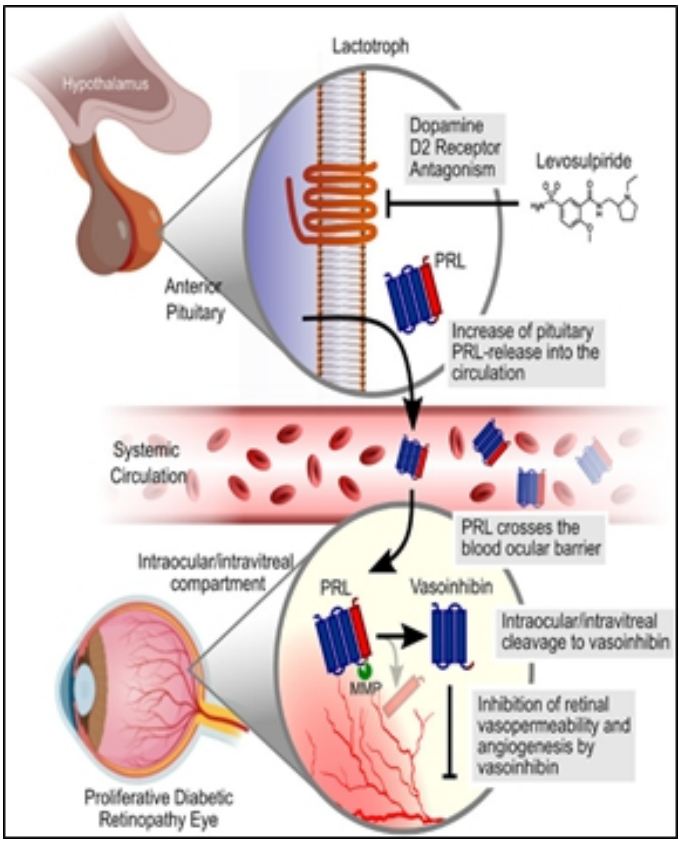


ACTION OF LEVOSULPIRIDE IN DIABETIC RETINOPATHY

The circulating levels of vasoinhibin are reduced in patients with diabetic retinopathy and studies have shown that the elevation of systemic PRL results in the accumulation of vasoinhibin in the retina capable of inhibiting the vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), thus inhibiting diabetes induced retinal vaso-permeability and ischemia induced retinal angiogenesis.

Levosulpiride, a prokinetic, frequently used to treat diabetic gastroparesis, is a potent inhibitor of dopamine D2 receptors in the anterior pituitary causing a therapeutic effect (anti-emetic effect) as well as increase in the serum PRL levels since dopamine is the main endogenous inhibitor of prolactin synthesis and secretion at the gastrointestinal and anterior pituitary levels.

Levosulpiride by increasing serum PRL levels, increases the conversion to its bioactive vasoinhibin in the vitreous of proliferative diabetic retinopathy patients, which may help counteract the disease progression.



In a clinical study conducted on male and female type 2 diabetic patients with proliferative diabetic retinopathy, the patients were divided to receive either placebo or 25mg TID of levosulpiride for one week before vitrectomy and clinical parameters including PRL levels were evaluated.

The serum & vitreous PLR levels observed were 11-fold higher & 2-fold higher respectively in patients receiving levosulpiride as compared to placebo.

Vasoinhibin from the vitreous from levosulpiride-treated patients inhibited the VEGF- and bFGF-induced endothelial cell proliferation, whereas PRL from placebo-group had no effect. This proved that the vasoinhibin and not the PRL inhibited the VEGF- and bFGF-induced endothelial cell proliferation.

These findings suggested that levosulpiride-induced hyperprolactinemia causes the accumulation of vasoinhibin in the vitreous of PDR patients, which inhibits endothelial cell proliferation.

Source: Nunez-Amano CD et al. Transl Vis Sci Technol 2020; 9(():27, Nunez FF et al. Investigative Opthalmology & Visual Science 2020; 61(7): 4958, Triebel J et al. Front Endocrinol 2017; 8(342): 1-7.

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