Antihyperalgesic Activity in Diabetes Induced Neuropathy

Nandita Avinash Ranbhise*, Prof. D.G.Joshi

Vansantidevi Patil Institute of Pharmacy, Kodoli.

Tal. Panhala, Dist. Kolhapur, (M S), India.

www.ijppr.humanjournals.com

ABSTRACT

The term diabetes mellitus describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long term damage, dysfunction and failure of various organs. Diabetes mellitus is a major and growing health problem in most countries and an important cause of prolonged ill health and early death. Diabetes has now become a global public health burden with worldwide incidence of 5% in the general population. The long term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction. One of the most common diabetes-related complication is diabetic neuropathy which affects nearly 50% to 66% of all diabetic patients and affects individuals with both type 1 and type 2 diabetes. Tricyclic antidepressants are considered the first-line choice of treatment for chronic pain associated with diabetic neuropathy. Neuropathic pain generally responds quickly to tricyclic antidepressants and often requires one third to one half the dosage administered in treatment of depression. Lacosamide a novel chemical entity with anticonvulsant and analgesic properties is being developed to treat epilepsy and neuropathic pain conditions.

INTRODUCTION

Diabetes mellitus is a major and growing health problem in most countries and an important cause of prolonged ill health and early death [1]. Diabetes has now become a global public health burden with worldwide incidence of 5% in general population. In USA, which ranks third after India and China in the prevalence of diabetes, the growth rate is expected to be much smaller: from 13.9 million in 1995 to 21.9 in 2025.

The rise in number of people with diabetes is expected to be fast in Pakistan, Indonesia, Egypt and Mexico, and Japan [2]. The countries with the largest number of diabetic people in the year 2025 will be China and United States [3]. The number of adults with diabetes in the world will rise from 135 million in 1995 to 300 million in the year 2025. Recent studies of geographical and ethnical influences have shown that people of Indian origin are highly prone to diabetes[4]. There are more than 30 million people with diabetes mellitus in India and the incidence is increasing. Also, there are many patients in the community with undiagnosed diabetes. The number of adults suffering from diabetes in India is expected to increase three-fold, from 19.4 million in 1995 to 57.2 million in 2025 [5].

Diabetes is being projected as the World's main disabler and killer in the next 25 years. The real burden of this disease is however due to its associated complications which lead to increased morbidity and mortality. The long term effects of diabetes mellitus include progressive development of specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease.

One of the most common diabetes-related complication is diabetic neuropathy which affects nearly 50% to 66% of all patients with diabetes and affects individuals with both type 1 and type 2 diabetes. The morbidity and mortality rates with diabetic neuropathy are highest as compared with other complications of diabetes. Overall, approximately 10% of the patients with diabetes experience persistent pain from neuropathy. The pain can be ongoing, spontaneous or hyperalgesic i.e., increased response to painful stimulus.

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

306

Tricyclic antidepressants are considered the first-line choice of treatment for chronic pain associated with diabetic neuropathy. Neuropathic pain generally responds more quickly than depression to tricyclic antidepressants and often with one third to one half the dosage administered for depression. Its antidepressant effect is due to inhibition of reuptake of serotonin and / or nor epinephrine by neuronal membranes.

Anticonvulsant drugs are having analgesic properties that are being developed to treat epilepsy and neuropathic pain conditions. Lacosamide for example has shown efficacy in many animal models of chronic pain and in several short and long term Phase II/III clinical trials in humans with diabetic neuropathic pain. The mechanism of action of lacosamide used to treat neuropathic pain is that it selectively enhances sodium channel slow inactivation without affecting fast inactivation and may modulate collapsin-response mediator protein2 [6,7,8].

Diabetic Neuropathy

Diabetic neuropathy (DNP) refers to a group of debilitating, diabetes-related nerve disorders. DNP is a descriptive term that encompasses a spectrum of clinical and subclinical syndromes with differing anatomical distributions, clinical courses, and possibly differing underlying pathogenetic mechanisms. Each one of them is characterized by diffuse or focal damage to peripheral, somatic or autonomic nerve fibers resulting from diabetes mellitus [9].

Diabetic neuropathy is common, related to increased morbidity and mortality, and has no effective treatment at present. Interventions based on putative pathways thought to contribute to damage and repair of nerve fibres have yielded little success to date. Pain is a potentially debilitating manifestation of diabetic neuropathy. A better understanding of the mechanisms leading to nerve fibre degeneration and regeneration as well as pain has recently resulted in the development of a more targeted approach to the treatment of diabetic neuropathy [10].Diabetic neuropathies can be classified as reversible or chronic. The most common type is the chronic, progressive distal symmetric polyneuropathy where sensory symptoms in the lower limbs dominate. Autonomic neuropathy is often a feature of progressive polyneuropathy, but is rarely symptomatic. Mononeuropathies affecting femoral, truncal or ocular nerves are among the reversible neuropathies of diabetes.

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

307

The prevalence increases with duration of disease as well as with poor glycaemic control, height, and age. The pathogenesis of diabetic neuropathies is not clear, but possibly involves a complex of metabolic factors inducing nerve ischemia.

Tight glycaemic control has been shown to protect against or delay the occurrence of neuropathy. Tricyclic antidepressants are still the drugs of choice against painful diabetic neuropathy, but gabapentin and tramadol are new alternatives [11].

Classification of Diabetic Neuropathy

Since the precise aetiopathogenesis of diabetic neuropathy is not well defined, it becomes difficult to classify the types. Thomas reported a simple classification based on anatomical characteristics in Diabetic neuropathy as follows;

Diabetic neuropathies:

A. Diffuse

1. Distal symmetric sensori-motor polyneuropathy

2. Autonomic neuropathy:

a. Sudomotor

b. Cardiovascular

c. Gastrointestinal

d. Genitourinary

3. Symmetric proximal lower limb motor neuropathy (amyotrophy)

B. Focal

1. Cranial neuropathy

2. Radiculopathy/plexopathy

3. Entrapment neuropathy

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

308

4. Asymmetric lower limb motor neuropathy (amyotrophy)

a. Distal symmetric polyneuropathy

Distal symmetric polyneuropathy is the most common and widely recognized form of DNP. It may be either sensory or motor, and involve small fibers, large fibers, or both. Small nerve fiber dysfunction usually occurs early and often is present without objective signs or electrophysiologic evidence of nerve damage [12]. It is manifested early with symptoms of pain and hyperalgesia in the lower limbs, followed by a loss of thermal sensitivity and reduced light touch and pinprick sensation [13]. There are, however, a variety of ways in which small-fiber neuropathies can be present. Clinical manifestations of small-fiber neuropathies include the following:

- Pain of the C-fiber type is burning, superficial and associated with allodynia (i.e., interpretation of all stimuli as painful).
- Late in the condition there is hypoalgesia.
- Decreased sweating, dry skin, impaired vasomotion, impaired blood flow and a cold foot.
- There is remarkable intactness of reflexes, motor strength, loss of cutaneous nerve fibers.

b. Proximal motor neuropathy (diabetic amyotrophy)

It may be symmetrical or asymmetrical, and with or without sensory loss. Patient usually presents with difficulty in getting up from squatting position, pain in climbing stairs and marked weight loss (sometimes upto 40% of original weight). It predominantly affects anterior (quadriceps) and adductor compartments of thigh. Wasting and weakness of quadriceps is so severe that the knee often gives way, and patient may fall.

c. Autonomic neuropathy

Any organ of body which is supplied by autonomic nerves can be affected. Symptoms of autonomic neuropathy range from minor to severe. The severe form may affect survival and can cause sudden death. Among autonomic neuropathic symptoms gustatory sweating is most common, followed by postural hypotension and diarrhea. Loss of sweating in the feet, sexual dysfunction, bladder abnormalities, and gastroparesis may also occur [14].

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

309

Symptoms and signs of autonomic neuropathy

✓ Cardiovascular:

Postural hypotension, resting tachycardia, painless myocardial infarction, sudden death (with or without association with general anaesthesia.

✓ Gastrointestinal:

Oesophageal motor incoordination, gastric dysrhythmia, hypomotility (gastroparesis diabeticorum), pylorospasm. Uncoordinated intestinal motility (diabetic diarrhoea, spasm), intestinal hypomotility (constipation), gall bladder hypocontraction (diabetic cholecystopathy), anorectal dysfunction (faecal incontinence).

✓ Genitourinary:

Diabetic cystopathy (impaired bladder sensation, atonic bladder, post micturition dribbling, detrusor hyporeflexia or hyperreflexia), male impotence, ejaculatory disorders, reduced vaginal lubrication, dyspareunia.

✓ Respiratory:

Impaired breathing control, sleep apnoea, thermoregulatory, sudomotor, vasomotor.

✓ Pupillary:

Miosis, disturbances of dilatation, argyll robertson pupil.

d. Focal neuropathies or mono-neuropathies

The diabetic patients are also susceptible to a variety of asymmetric and focal neuropathies.

i) Cranial Neuropathy:

The third, fourth, and sixth cranial nerves are commonly involved. The third cranial nerve palsy presents with eye pain, diplopia, and ptosis but pupillary response to light is usually spared.

ii) Truncal Neuropathy:

It usually presents with gradual onset of pain and dysaesthesia in the lower anterior chest or upper abdomen with nocturnal intensification. On examination, hypoaesthesia or hyperaesthesia

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

310

may be present in the appropriate thoracic segment and abdominal muscle weakness leading to abdominal swelling. A careful sensory examination of abdomen and thorax is mandatory in a diabetic person presenting with unexplained thoracoabdominal pain [14].

iii) Entrapment neuropathy:

Also known as pressure palsy. Median nerve is mostly affected and is secondary to soft tissue changes associated with limited joint mobility. Occasionally ulnar or lateral cutaneous nerve of thigh may also be affected [14].

Pain in diabetic neuropathies

Neuropathic pain is defined as the one resulting from an injury to the nervous system, and diabetic neuropathy is one of the most important complication of diabetes. As well as other neuropathic pain syndromes, painful diabetic neuropathy is associated with clinical symptoms like tactile allodynia (nociceptive responses to normally innocuous stimuli), hyperalgesia augmented pain response to normally painful stimuli) and spontaneous pain [15].

Overall, approximately 20-24% of patients with diabetes experience neuropathic pain. Pain syndromes that last less than 6 months to a year are classified as acute whereas pain syndromes lasting longer than 6 months to a year are classified as chronic [13]. The pain can be ongoing; spontaneous; or hyperalgesic (i.e., increased response to a painful stimulus). It can be severe and sometimes intractable. Pain may be stimulus-independent or stimulus-evoked.

Table 1. Sensory signs and symptoms of stimulus-independent and stimulus-evoked pain

Stimulus independent pain	Stimulus evoked pain
Involves continuous burning sensation, intermittent shooting, lancinating sensations, electric-shock–like pain, dysesthesias	Pain after mechanical, thermal, or chemical stimulation, includes hyperalgesia or allodynia

Most of our understanding of pain mechanisms derives from basic research, including *in-vivo* and *in-vitro* cellular and molecular studies. Although this research has led to an enormous

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

311

increase in our knowledge, these data need to be interpreted with care because of the limitations associated with preclinical studies. For example, there are difficulties in translation from animal behavior to human pain sensation. There exist few long-term data that correlate with the chronic time scale of human pain to distinguish between acute injury-related adaptive changes and pathological dysfunction leading to chronic pain states. Nevertheless, pain research in human beings has progressed immensely over the past decade, and results from quantitative sensory testing, questionnaires, skin punch biopsies, functional imaging, and experimental human pain models have provided us with further insights into human pain pathology. Exchange of information between basic and clinical research is essential to determine the clinically important pain pathology. So far, both basic and human research indicates that a lesion of afferent pathways is necessary for development of neuropathic pain. Furthermore, data clearly indicate that not one but several mechanisms can lead to neuropathic pain. Importantly, many of these mechanisms do not depend on the cause of the disease: the same mechanism can be found in different diseases (eg, in post-therapeutic neuralgia and in painful polyneuropathy). In one individual patient, different mechanisms might be involved and which could lead to the same symptom. This not only indicates the complexity of neuropathic pain, but also highlights the clinical importance of identifying underlying pain mechanisms in individual patients. Because different treatment regimens are needed for different pain mechanisms, a mechanism-based treatment approach can lead to efficient analgesia. One way to progress at this point in research and in the clinic is to hypothesis that pain mechanisms can be identified by analysing patient's individual symptoms and signs with the above-mentioned methods. By analyzing the effect of treatment that targets these suggested pain mechanisms, the concept of mechanism-based treatment can be verified (see section below on specific sensory profiles). Such an approach will enable design of large controlled trials that are more focused on treating mechanism-related symptoms and signs instead of etiology-based studies. At present, the available data can help to understand the associations between at least some clinical symptom ms and suggested underlying mechanisms.

o **Ectopic nerve activity**

Sensing ongoing spontaneous pain and paroxysmal shooting pain in the absence of any external stimulus is caused by ectopic impulse generation within the nociceptive pathways. Such

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

312

spontaneous ectopic activity has been recorded by miconeurography in afferent fibers from a neuroma in patients with stump and phantom pain, as well as in patients with painful diabetic neuropathy. Under physiological conditions, activation of unmyelinated (C-fibre) and thinly myelinated (Aδ-fibre) nociceptive afferent fibres indicates potential tissue damage, which is reflected in the high thresholds of nociceptors for mechanical, thermal, and chemical stimuli. These conditions change dramatically in neuropathic pain states. After a peripheral nerve lesion, spontaneous activity is evident in both injured and neighbouring uninjured nociceptive afferents. Increasing levels of mRNA for voltage-gated sodium channels seem to correlate with ectopic activity, and increased expression of sodium channels in lesioned and intact fibres might lower action potential threshold until ectopic activity takes place. Similar changes within second-order nociceptive neurons are thought to occur after central lesions, leading to central neuropathic pain. Further evidence for the crucial role of voltage-gated sodium channels in chronic pain states comes from patients with erythromelalgia and paroxysmal extreme pain disorder who have severe ongoing pain at different sites of the body. These hereditary disorders are caused by gain-of-function mutations in the SCN9A gene that encodes the Nav1.7 voltage-gated sodium channel. Microneurographic recordings have indicated ongoing ectopic activity of nociceptive afferents in these patients after increased membrane excitability: this activity is not associated with any direct nerve lesion but is caused by underlying pain channelopathies.

o **Pain presentation as a confounding issue**

The presentation and character of pain in DNP can be highly diverse which typically worsens at night [13]. Krause and Backonja defined neuropathic pain as ''a group of disorders characterized by pain due to dysfunction or disease of the nervous system at a peripheral level, a central level, or both.'' Neuropathic pain can manifest as stimulus-independent pain or as stimulus-evoked or stimulus-dependent pain, whose underlying mechanisms are likely to differ.

Similarly, the mechanisms responsible for hyperalgesia and allodynia differ. Hyperalgesia is defined as increased pain response to a normally painful stimulus. Allodynia is said to occur when pain is provoked by a stimulus not normally painful. This is related to the different nerve pathways implicated in these various categories. For example, aberrations of the C and A delta-fibers may result in the burning or prickling sensations of stimulus-independent pain or of

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

313

hyperalgesia. Under pathologic conditions, touch-sensitive a beta-fibers may cause stimulus-independent dysesthesias or paresthesias or stimulus-evoked allodynia.

Peripheral sensitization and central sensitization processes in peripheral nociceptors leads to spontaneous burning pain, static mechanical hyperalgesia, and heat hyperalgesia. This spontaneous activity in nociceptors induces secondary changes in the central sensory processing, leading to spinal cord hyperexcitability that causes input from mechanoreceptive A beta-fibers (light touching) and A delta-fibers (punctuate stimuli) to be perceived as pain (dynamic and punctuate mechanical allodynia) [13].

o **Different mechanisms of pain and there possible treatment:-**

(a) Central terminals of c-afferents project into the dorsal horn and make contact with secondary pain-signaling neurons. Mechanoreceptive Ab afferents project without synaptic transmission into the dorsal columns (not shown), and also contact secondary afferent dorsal horn neurons.

(b) Spontaneous activity in peripheral nociceptors (peripheral sensitization, black stars) induces changes in the central sensory processing, leading to spinal cord hyperexcitability (central sensitization, white star) that causes input from mechanoreceptive Aβ (light touch) and Aδ fibers (punctuate stimuli) to be perceived as pain (allodynia).

(c) C-nociceptor degeneration and novel synaptic contacts of Ab fibers with 'free' central nociceptive neurons, causing dynamic mechanical allodynia.

(d) Selective damage of cold-sensitive Ad fibers that leads to central disinhibition, resulting in cold hyperalgesia.

o **Central sensitization**

Secondary allodynia and hyperalgesia (i.e., evoked pain, in particular dynamic mechanical allodynia) in the area adjacent to the innervations territory of the lesioned nerves requires involvement of the CNS. Central sensitization might develop as a consequence of ectopic activity in primary nociceptive afferent fibers and structural damage within the CNS itself might not be necessarily involved. Ongoing discharges of peripheral afferent fibers that release excitatory amino acids and neuro-peptides within the dorsal horn of the spinal cord lead to

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

314

postsynaptic changes of second-order nociceptive neurons, such as phosphorylation of NMDA and AMPA receptors or expression of voltage-gated sodium channels. These changes induce neuronal hyper excitability that enables low-threshold mechanosensitive Aβ and Aδ afferent fibres to activate second-order nociceptive neurons. This means that normally innocuous tactile stimuli such as light brushing or pricking the skin become painful. Similar mechanisms might take place not only within the spinal cord, but also at supraspinal levels, as has been reported in patients with central pain.

- **Mechanisms contributing to ectopic nerve activity and central sensitization:**

Further pathophysiological mechanisms involved in neuropathic pain contribute to ectopic activity and central sensitization. Inflammation after a nerve lesion induces activation and migration of macrophages into the nerve and dorsal root ganglion, which contribute to pain hypersensitivity by releasing pro-inflammatory cytokines, including tumour necrosis factor α. After peripheral and central nerve lesions, activated microglia within the CNS release several immune modulators that also maintain neuropathic pain. These inflammatory processes, as well as other changes within the milieu of the peripheral nerve endings, contribute to peripheral sensitization (i.e., decreased activation thresholds and increased membrane excitability). Similar to central sensitization, peripheral sensitization can also occur in intact nociceptors without any underlying nerve damage; however, in combination with lesion-related pathological receptor expression, ectopic activation can be facilitated and maintained. After a peripheral nerve lesion, there is a loss of inhibitory GABAergic interneurons in the spinal horn. Prevention of cell death of interneurons attenuates mechanical and thermal hyperalgesia, indicating that disinhibition contributes to neuropathic pain. Further potent inhibitory neurons, such as descending pathways originating in the brainstem, contribute to modulation of pain processing. Lesions that affect these opiodergic and monoaminergic systems also lead to pain exacerbation via disinhibition. Another suggested form of disinhibition is the underlying mechanism of cold hyperalgesia, which is present in 23% of patients with central post-stroke pain after lesions of innocuous cold conducting fibre afferents. According to the thermosensory disinhibition theory of Craig, these afferents normally inhibit cold-activated pain pathways. In some cases of amputations, postherpetic neuralgia, complex regional pain syndromes, and post-traumatic neuralgias, topical administration of norepinephrine and enhancement of physiological sympathetic activity

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

315

increased spontaneous pain and dynamic mechanical hyperalgesia. This finding indicates a pathological adrenergic coupling between sympathetic postganglionic fibres and nociceptive afferent fibres, which might result from expression of α-receptors on cutaneous afferent fibres or from sprouting of sympathetic fibres within the dorsal root ganglion. Consequently, this symptom of sympathetically maintained pain can be treated by use of sympathetic blocks.

o **Prevalence of Diabetic Neuropathy**

Diabetic neuropathy can afflict any nerve in the body, including those of the autonomic nervous system. A diverse range of symptoms are associated with diabetic neuropathy, including pain, numbness, tingling, digestive disturbances, bladder problems, and impaired cardiovascular regulation, among others. Lack of awareness of hypoglycaemia, due to neuropathy within the autonomic nervous system, is particularly dangerous for insulin-requiring patients with diabetes.

As many as 60–70% of people with diabetes may develop some degree of neuropathy, and this condition is responsible for more than 60% of non-traumatic lower limb amputations in people with type 2 diabetes [16].Considering the high prevalence rate of above diabetic complications, in the present study, we have concentrated on; diabetic neuropathic pain. Neuropathic pain is generally considered to be one of the most troublesome complication of diabetes and it is sometimes particularly insensitive to drug therapy.

Tricyclic antidepressants are most widely used drugs for diabetic neuropathic pain particularly amitriptyline apart from its actions at the spinal and supraspinal sites, amitriptyline is now known to act at peripheral sites [17]. Involvement of an endogenous adenosinergic system in the peripheral effect of amitriptyline has been shown for inflammatory and neuropathic pain models [17].

Lacosamide has been shown to be active in animal models for neuropathic and inflammatory pain models. In addition, oral lacosomide produced analgesia in an open label study of 25 adult human subjects with resistant neuropathic pain.

o **Management of neuropathic pain**

Pain control

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

316

Control of pain constitutes one of the most difficult management issues in DNP. If, however, pain is divided according to its derivation from different nerve fiber type (A delta versus C fiber), spinal cord, or cortical, then different types of pain respond to different therapies [13].

Symptomatic treatment

Pain is the most common symptom, which could be superficial, deep, or aching. The management of pain is often difficult and disappointing. There is no single correct approach to the management of any given patient with peripheral neuropathy. Often it requires patience on the part of patient and physician who must try a variety of different medications on a trial and error basis until a satisfactory regimen is established.
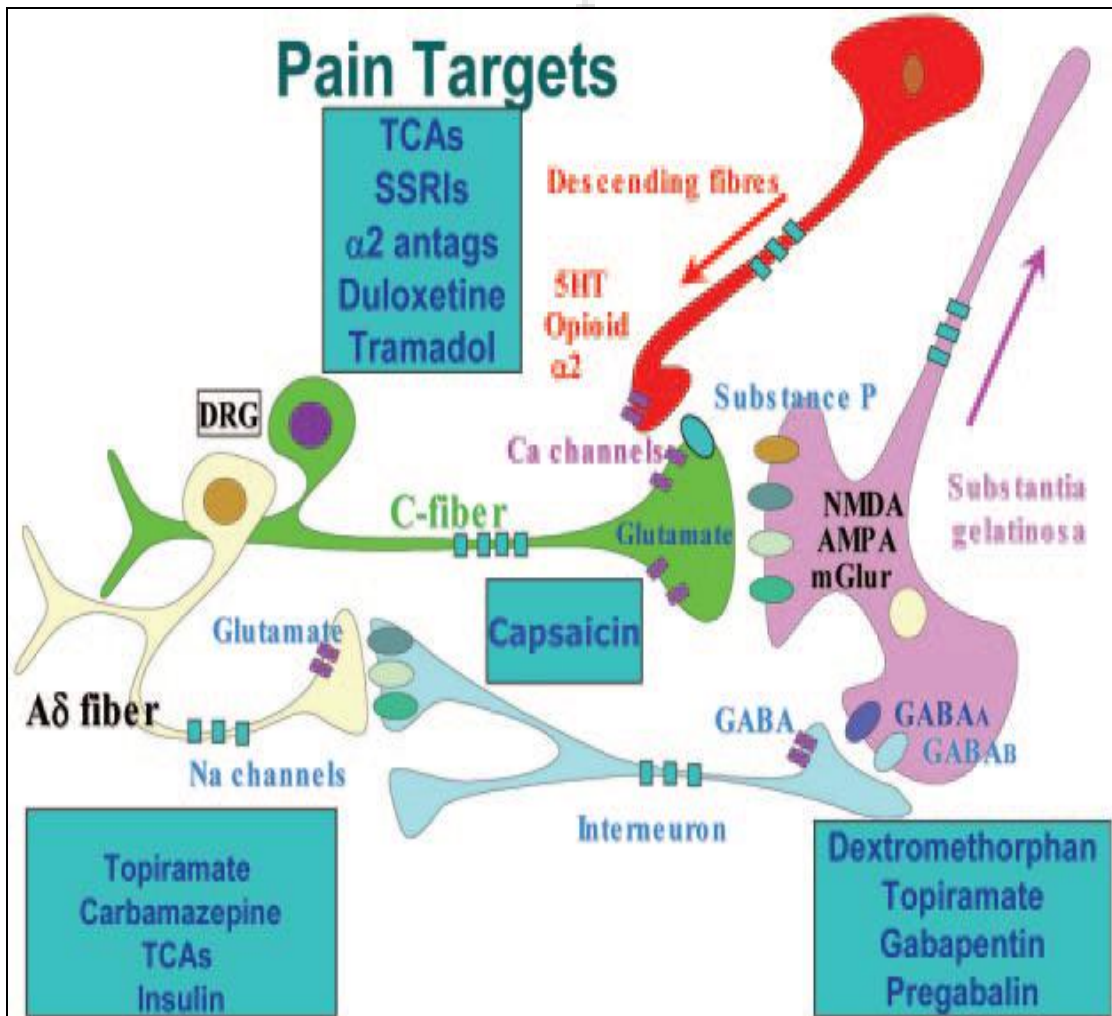

Figure no. 1. Pain Targets

C fibers are modulated by sympathetic input with the spontaneous firing of different neurotransmitters to the dorsal root ganglia (DRG), spinal cord and cerebral cortex. Sympathetic blockers (clonidine) and depletion of axonal substance P (SP) used by C-fibers as their neurotransmitter (capsaicin) may improve pain. In contrast Ad fibers utilize sodium (Na) channels for their conduction and agents that inhibit sodium exchange such as antiepileptic drugs, tricyclic antidepressants (TCAs) and insulin may ameliorate this form of pain. Anticonvulsants (carbamazepine and topiramate) potentiate g-aminobutyric acid (GABA) activity, inhibit sodium and calcium (Ca) channels and inhibit N-methyl-D-aspartate (NMDA) and a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. Pregabalin appears to modulate the a2 d1 subunit of the calcium channel on presynaptic neurons, decreasing the release of excitatory neurotransmitters. Dextromethorphan blocks NMDA receptors in the spinal cord. TCAs, selective serotonin reuptake inhibitors (SSRIs) and serotonin and reuptake inhibitors (SNRIs) inhibit serotonin and norepinephrine reuptake, enhancing their effect in endogenous pain-inhibitory systems in the brain. Tramadol is a central opioid analgesic.

Tricyclic antidepressants are most widely used drugs for diabetic neuropathic pain particularly amitriptyline apart from its actions at the spinal and supraspinal sites, amitriptyline is now known to act at peripheral sites [17]. Involvement of an endogenous adenosinergic system in the peripheral effect of amitriptyline has been shown for inflammatory and neuropathic pain models [17]. The mechanism of action of anticonvulsant used to treat neuropathic pain is that it selectively enhances sodium channel slow inactivation without affecting fast inactivation and may modulate collapsin-response mediator protein2 [6,8].

Animal models used to induce diabetes and diabetic complications:

Spontaneous type 2 diabetic models

Spontaneously diabetic animals of type 2 diabetes obtained from the animals with one or several genetic mutations transmitted from generation to generation (e.g., ob/ob, db/db mice) or by selected from non-diabetic outbreed animals by repeated breeding over several generation [e.g., GK rat, Tsumara Suzuki Obese Diabetes i.e. TSOD mouse] [18].

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

318

Spontaneous type 2 diabetic obese models

ob/ob mouse, db/db mouse, KK mouse, KK/Ay mouse, New Zealand Obese (NZO) mouse, NONcNZO10 mouse, TSOD mouse, M16 mouse, Zucker fatty rat, Zucker diabetic fatty rat, SHR SHR/N- cp rat, OLETF rat, Obese rhesus monkey (Macaca mullata) [19].

Spontaneous type 2 diabetic non obese models

Cohen diabetic rat, GK rat, Torri rat, Non obese mutant C57 BL/6 (Akita) mouse, ALS/Lt mouse.

Dietary or nutrition induced type 2 diabetic models

Sand rat, Tuco-Tuco and Spiny mouse are important models of nutritionally induced obesity and type 2 diabetes [20].

Chemically induced diabetic models

Chemically induced models of diabetes are common in elucidating the possible role of environmental factors involved in the endocrine pancreatic destructive processes and subsequent development of diabetes.

Obese models

Goldthioglucose obese diabetic mouse

Type 2 diabetes with obesity is induced in mice by goldthioglucose (150-350 or 200 mg/kg, i.p.) injection. Mice gradually develop obesity, hyperinsulinaemia, hyperglycaemia, insulin resistance over a period of 16- 20 week after goldthioglucose injection [21].

Non obese models

a. Alloxan (AL) induced diabetes in animals

Alloxan are by far the most frequently used drugs and this model has been useful for the study of multiple aspects of the disease. AL is the most prominent diabetogenic chemicals in diabetes research. In 1943, AL became of interest in diabetes research when Dunn and McLetchie reported that it could induce diabetes in animals as a result of the specific necrosis of the pancreatic β cells. The chemistry of AL and its derivatives.
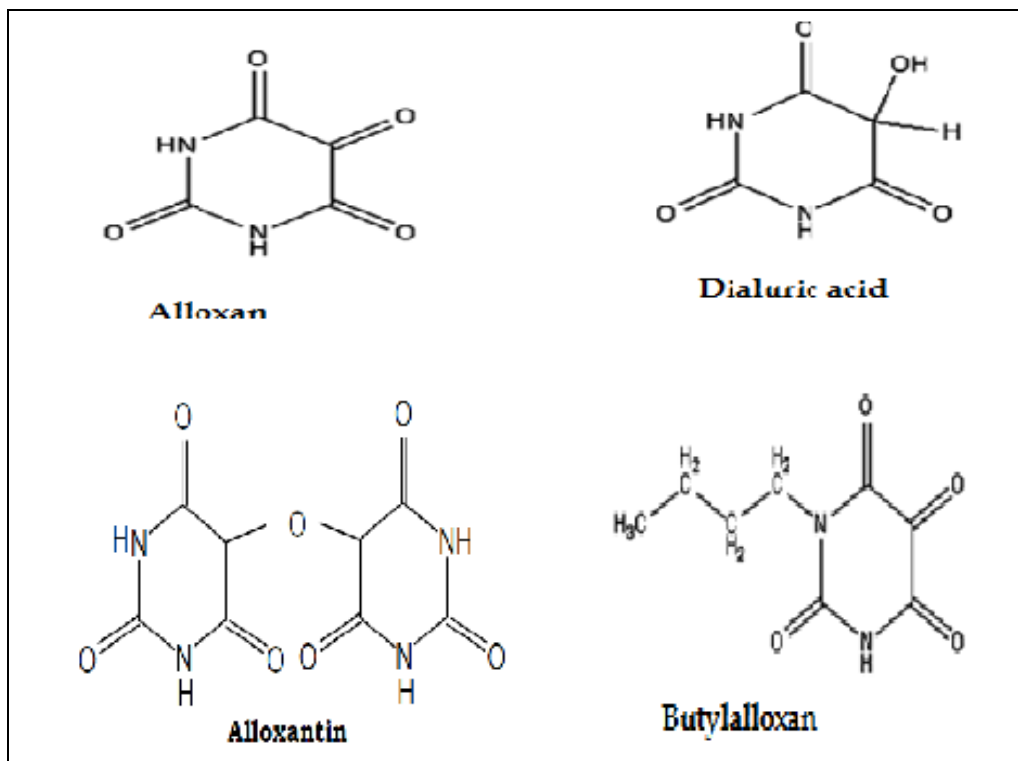
Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

319

Figure no. 2. Structure of alloxan and its derivatives

Alloxan (AL) is a β-cytotoxin, chemically called mesoxalylurea, messoxalyurea, mesoxalylcarbamide, and 2, 4, 5, 6-tetra-oxohexahye- 4-pyrimidine tetrone has been extensively used for in vivo induction of 'chemical diabetes' in animals. AL causes diabetes in animals through its ability to destroy the insulin-producing β cells of the pancreas. AL is a hydrophilic compound, which readily decomposes at neutral pH [22].It inhibits thiol-dependent enzymes such as glucokinase and hexokinase and undergoes redox cycling in the presence of physiological reducing agents, generating 'active oxygen' species. It is generally believed that the later species are involved in the initiation of the toxic changes that leads to pancreatic β cell death. AL and N substituted AL derivatives were selectively toxic to pancreatic β cells, with other endocrine cells and exocrine parenchymal cells being well preserved, even at high concentration.

Mechanism of action: AL and the product of its reduction, dialuric acid, establish a redox cycle with the formation of superoxide radicals. These radicals undergo dismutation to hydrogen peroxide with a simultaneous massive increase in cytosolic calcium concentration, which causes rapid destruction of pancreatic β cells. The most frequently used intravenous dose of AL in rats is 65 mg/kg, but when it is administered intraperitoneally (i.p.) or subcutaneously its effective

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

320

dose must be higher. For instance, an intraperitoneal dose below 150 mg/kg may be insufficient for inducing diabetes. In mice, doses vary among 100–200 mg/kg by intravenous route (i.v.). Guinea pigs, ducks, owl, chicks, frogs and toads are resistant to the diabetogenic action AL [22].

b. Streptozotocin (STZ) induced diabetes in animals

Streptozotocin is a nitrosourea analogue in which the N-methyl-N-nitrosourea moiety is linked to the carbon-2 of a hexose. It is an antimicrobial agent and has also been used as a chemotherapeutic alkylating agent. The potential problem with STZ is that its toxic effects are not restricted to pancreatic β cells since it may cause renal injury oxidative stress inflammation and endothelial dysfunction. The destruction of pancreatic β cells by STZ is associated with a huge release of insulin which makes animals more susceptible to severe hypoglycemia that may be lethal. Besides rats, dogs and mice other animal species such as rabbits and monkeys have been employed to induce diabetes by these protocols, but rabbits and pigs are more resistant to STZ.
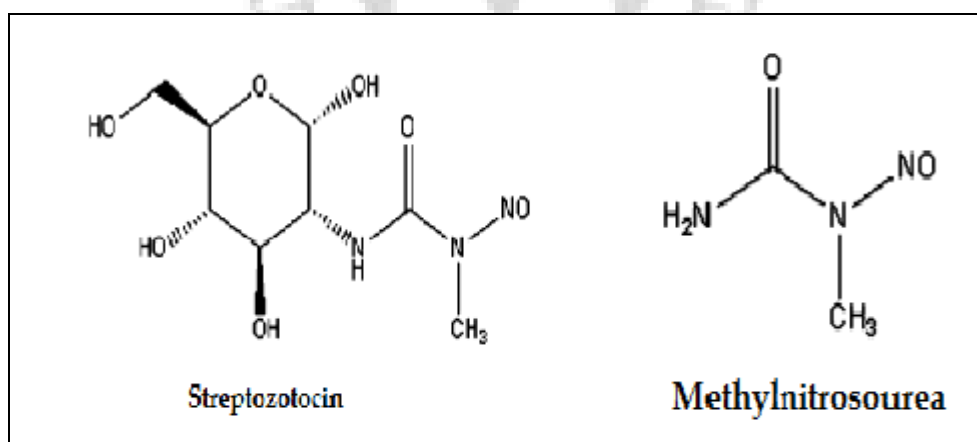

Figure no. 3. Structure of streptozotocin and its derivatives

c. STZ-Nicotinamide induced diabetes in animals

Since injection of nicotinamide, a precursor to NAD, immediately before, or soon after, the administration of streptozotocin completely protects against the development of diabetes. It was postulated that streptozotocin acts on the β cell by depletion of islet NAD. As NAD is an antioxidant which exerts protective effect on the cytotoxic action of STZ by scavenging free radicals and causes only minor damage to pancreatic β cell mass producing type 2 diabetes.

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

321

d. Neonatal STZ induced diabetes in animals

STZ when injected neonatally or immediately after birth, rats develop type 2 diabetes in the adult age. Single injection of STZ at the dose range of 80-100 mg /kg of STZ (i.v. or i.p. or s.c.) to one or two or five day old Wistar or Sprague-Dawley neonatal rats has been reported to produce type 2 diabetic conditions. Some investigators have also developed neonatal type 2 diabetic models by injecting AL (200 mg/kg, i.p.) to male neonatal rats at age of 2, 4 or 6 day after birth and found to be much useful for the investigation of long term complication of type 2 diabetes.

e. STZ with high fat or high fructose diet

Feeding of high fat or high fructose diet with STZ treatment produces hyperinsulinaemia and insulin resistance initially followed by treatment with STZ that causes the β cell damage and frank hyperglycaemia in the presence of almost absolute normal insulin circulating concentrations in nongenetic, outbred animals such as and mice.

o   **Preclinical evaluation models for diabetic neuropathy**

Diabetic neuropathy is a heterogeneous disorder that may affect sensory, motor, and autonomic nerves. The commonest type is a symmetric distal sensorimotor polyneuropathy, in which pain is a predominant symptom. The pathogenesis of diabetic neuropathic pain remain enigmatic, in spite of several suggested mechanisms been proposed. These include axonal degeneration/regeneration, neuroma properties, which cause ectopic impulse generation and ephaptic transmission, small-fiber diseases, which involve the A delta and C-fiber, dorsal root ganglion involvement, central sensitization and neural plasticity.

When nerve fibers undergo active degeneration or impaired regeneration, exerts exciting impulses, thus inducing subjective symptoms such as pain or paresthesia (positive symptoms). Once nerve fibers are lost, then the loss of sensation will take place. With increasing loss of fibers, the area of sensory loss or its severity will be augmented (negative symptoms). Diabetic neuropathy is usually observed with signs like thermal/mechanical hyperalgesia, dynamic/thermal allodynia. Hot plate test, warm plate test, tail flick test, mechanical paw pressure test and test for dynamic allodynia are mostly used preclinical models for assessment of diabetic neuropathy. Sciatic nerve tissue antioxidant assays are also preferred preclinical

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

322

biochemical estimation because increased oxidative stress as a result of hyperglycemia is considered to be responsible for the nerve dysfunction.

Thermal (hot plate, tail immersion tests) / mechanical hyperalgesia (Randall–Selitto test)

Decrease in pain threshold in the following mentioned tests is an indication of C-fibre and A-delta fiber nerve degeneration/regeneration which results in hyperagesia [13].

a) Hot plate test: Keep animals individually on hot plate analgesiometer adjusted to temperature of 55 ± 1^0C. Record the latency to the first sign of paw licking or jump response to avoid the heat as an index of the pain threshold (cut-off time was 10 seconds) [23].

b) Tail immersion (hot water) test: Immerse the tail of animal in a hot water bath (52.5 ± 0.5^0C) until tail withdrawal (flicking response) or signs of struggle are observed (cut-off 12 seconds) [23].

c) Paw pressure withdrawal test: Apply increasing pressure at a linear rate with cut-off of 250 g to the center of the hindpaw of animal. When the animal displayed pain by withdrawal of the paw or vocalization or sign of struggling to avoid pain, register the applied paw pressure by an analgesia meter in mass units (grams). Reduction in paw withdrawal threshold is an indication of mechanical hyperalgesia [23].

Thermal (warm plate, tail immersion test)/dynamic (von Frey filament test) allodynia

Decrease in pain threshold in the following tests is an indication of touch sensitive A-beta fiber nerve degeneration/regeneration which results in allodynia [13].

a) Warm plate test: Keep animals individually on hot plate analgesiometer adjusted to temperature of 38^0C. Record the latency to the first sign of paw licking or jump response to avoid the heat as an index of the pain threshold (cut-off time was 30 seconds) [6].

b) Tail immersion (cold water) test: Immerse the tail of animal in a cold water bath (10 ± 0.5^0C) until tail withdrawal (flicking response) or signs of struggle are observed (cut-off 15 seconds) [23].

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

323

c) **Tail immersion (Hot water) test:** Tail of rat was marked at 5 cm from the tip and was immersed in a warm water bath (52.5±0.5°C) until tail withdrawal (flicking response) or signs of struggle were observed (cut-off 30 s). Shortening of the tail withdrawal time indicates hyperalgesia [23].

d) **Beam walk test:** Rats were allowed to walk from a start of platform along a ruler (60 cm long, 3 cm wide) elevated 60 cm above the bench by metal supports to a goal box (enclosed house). Three trials were performed for each rat and were designed such that the rat tested would be aware that there was a goal box that could be reached. A ruler was used because the rat found this easy to cross and at the same time it induced minimum anxiety. Once the rat had been tested on the ruler and they were moved immediately to the beam test. The beam was made of wood, 1cm in diameter, 60 cm long and elevated 60 cm above the bench by metal support. Rats that fell down were returned to the position they fell from, with a maximum time of 60 sec allowed on the beam. The measurements taken were the number of foot slips (one or both hind limbs slipped from the beam) [24].

CONCLUSION

Diabetic neuropathy encompasses a variety of forms whose impact ranges from discomfort to death. Neuropathic pain is the most common symptom associated with diabetic neuropathy. It is a type of persistent pain that arises from functional changes occurring in the pain sensory system after peripheral nerve injury. Diabetic neuropathy is usually observed with signs like thermal/mechanical hyperalgesia, dynamic/thermal allodynia. Beam walk test, Hot plate test, warm plate test, tail flick test, mechanical paw pressure test and test for dynamic allodynia are beneficial preclinical models for assessment of diabetic neuropathy. Review article highlights how the tricyclic antidepressants and anticonvulsants may be effective as antihyperalgesic in diabetic neuropathy.

REFERENCES

1. WHO, 2000, <http://www.wpro.who.int/themes_focuses/theme2/ focus4/them es2_ focus4burd en.asp>, accessed 10 March 2000.
2. King, H., Aubert, R., Herman, W., 1998. Global burden of Diabetes 1995-2025. *Diabetes Care.* 21, 1414-31.
3. Ramachandran, A., Snehalatha, C., Vishwanathan, V., 2002. Burden of type 2 diabetes and its complications: The Indian scenario. curr sci. 83(12), 1471-1476.

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

324

4. Shaw, J.E., Courten, M.P., Zimmet, P.Z., 1999. Diabetes in the New Millennium (eds Turtle, J. R., Kaneko, T. and Osato, S.) The Endocrinology and Diabetes Research Foundation of the University of Sydney, Sydney. 1–9.

5. Arunachalam, S., Gunasekaran S., 2002. Diabetes research in India and China today: From literature-based mapping to health-care policy. Curr sci. 82, 9.

6. Beyreuther B, Callizot N, Stohr T. Antinociceptive efficacy of lacosamide in a rat model for painful diabetic neuropathy, S.D (2006) 539: 64-70.

7. Wang, Z., Hsu, C., Huang, C., Yin, M., 2010. Anti-glycative effects of oleanolic acid and ursolic acid in kidney of diabetic mice. European Journal of Pharmacology. 628, 255–260.

8. Yuying Wang, Joel M, Brian W, Ki Duk Park, Sarah M. Wilson, Bo Wang, Rachel Hale,Samy Meroueh, Theodore R. Cummins and Rajesh Khanna. In Silico Docking and Electrophysiological Characterization of Lacosamide Binding Sites on Collapsin Response Mediator Protein-2 Identifies a Pocket Important in Modulating Sodium Channel Slow Inactivation, The Journal of Biological Chemistry, (2010) 285 (33): 25296–25307.

9. Edwards, J. L., Vincent, A. M., Cheng, H. T., Feldman, E. L., 2008. Diabetic neuropathy: Mechanisms to management. Pharmacology & Therapeutics. 120, 1–34.

10. Malik, Z.A., Singh, M., Sharma, P.L., 2011. Neuroprotective effect of Momordica charantia in global cerebral ischemia and reperfusion induced neuronal damage in diabetic mice. Journal of Ethnopharmacology. 133, 729–734.

11. Nøkleby, Berg, K., Julsrud, T., 2005. Diabetic neuropathy-a clinical review. tidsskr nor laegeforen. 125(12), 1646-1649.

12. Hansen, T., 2002. genetics of type 2 diabetes. curr sci. 83(12), 1477-82.

13. Vinik, A.I., Park, T.S., Stansberry, K.B. Review: Diabetic neuropathies. Diabetologia (2000)43: 957-973.

14. Bhadada, S.K., Sahay. R.K., Jyotsna, V.P., Agrawal, J.K. Diabetic Neuropathy: Current Concepts. Indian Academy of Clinical Medicine (2001) 2(4): 305-318.

15. Ulugol A, Hakan C, Karadag Tamer M, Zeki Firat Z, Aslantas A, Dokmeci I. Involvement of adenosine in the anti-allodynic effect of Amitriptyline in streptozotocin-induced diabetic rats, (2002) 328: 129–132.

16. Zimmet, P. Z.The pathogenesis and prevention of diabetes in adults. Diabetes Care.(1995)18: 1050-64.

17. Esser MJ, Sawynok J (2000) Caffeine blockade of the thermal antihyperalgesic effect of acute amitriptyline in a rat model of neuropathic pain. Eur J Pharmacol 399:131-139.

18. Bell, D., 1994. Stroke in the diabetic patient. Diabetes care. 17, 213-219.

19. Alan D. Lopez, Colin D. Mathers, Majid Ezzati, Dean T. Jamison, and Christopher J. L. Murray. Measuring the Global Burden of Disease and Risk Factors (1990–2001): 1-13.

20. Shafrir, E. (2003): Diabetes in animals: contribution to the understanding of diabetes by study of its etiopathology in animal models. In: Diabetes Mellitus, Porte, D., Sherwin, R.S., Baron, A. (Eds.), McGraw-Hill, ISBN 0838520413, New York, pp. 231–255.

21. Lee, B., Kassel, D.B., Asakawa, T., Takeuchi, K., Christopher, R.J., 2008. Pharmacokinetic, pharmacodynamics, and efficacy profiles of alogliptin, a novel inhibitor of dipeptidyl peptidase-4, in rats, dogs, and monkeys European Journal of Pharmacology. 589, 306–314.

22. Lenzen, S., 2008. The mechanism of alloxan and streptozotocin-induced diabetes. Diabetologia. 51, 216-226.

23. Kuhad. A, Chopra. K, Lycopene amoliorates thermal hyperalgesia and cold allodynia in STZ induced Diabetic rat.Indian Journal of Experimental Biology (2008) 46: 108-111.

24. Lisette Lezcano, Lourdes Pedre, Caridad Verdecia, Teresa Sánchez, Nancy Fuentes and Liliana Turner. Convenience of the traversal beam test modified to evaluate the model of Parkinson's disease in Rat lesioned in SNPC, Journal of Cell and Animal Biology (2009) 3 (9) : 145-151.

Citation: Nandita Avinash Ranbhise et al. Ijppr.Human, 2015; Vol. 4 (3): 305-325.

325