INTRODUCTION

Sildenafil citrate was originally discovered in 1991 as a treatment for angina. The drug marketed under the name Viagra and received the approval of food and drug administration (FDA) as a treatment for erectile dysfunction in March 1998. It is the first oral medication approved for ED treatment in the European Union ***(Kuan and Brock, 2002)***.

Boyce and Umland (2001) stated that Sildenafil citrate is a vasodilator medication which improve blood circulation to the penis, and enhance the effects of *nitric oxide*, the drug that relaxes the smooth muscle of the penis during sexual stimulation, allowing the penis to become engorged and achieve erection. They added that the average allowed dose of Viagra is 50 mg. that may be increased up to 100 mg and remains effective up to four hours.

Padma et al. (2002) added that Sildenafil citrate can treat erectile dysfunction caused by psychological conditions as depression.

Erectile dysfunction drugs can decrease the arterial blood pressure, so it has a hypotensive effects that aggravate physiologic nocturnal hypotension, especially if the patient takes other drugs with hypotensive effects ***(Hayreh et al., 1999).***

Shakir (2001) also mentioned that Viagra may trigger transient hypotension, so it is prescribed with a great caution in

men with a history of heart attack, arthrosclerosis, angina, arrhythmia, and chronic low blood pressure problems**.**

Clinical studies by ***Tracqui et al. (2002)*** shown that the major problem in those patients is that the drug builds up in the plasma of these patients to a concentration that is three to eight times much more than normal, so Viagra should not be taken more than once per day**.**

The United States Food and Drug Administration, and the World Health Organization recorded 86 cases of vision loss related to sildenafil therapy ***(Fraunfelder et al., 2006)*.**

Multiple studies have shown that there is a strong causal relation between usage of sildenafil citrate and development of non artertic anterior ischemic optic neuropathy NAION but those studies focused on the clinical findings only ***(Hayreh and Zimmerman, 2008).***

There are multiple types of Optic neuropathies which are:

1) Ischemic optic neuropathy

Osborne and Balcer (2013) stated that there are two types of Ischemic optic neuropathy in elderly: Anterior and Posterior. Both of them are divided into arteritic and non-arteritic forms.

A. Non-Arteritic Anterior Ischemic optic neuropathy (NAAION):

Purvin (2000) Described vascular occlusive disease or disorders that can reduce the circulation of blood in the short posterior ciliary arteries between the ages of 55 and 70 years.

B. Arteritic Anterior Ischemic Optic Neuropathy (AAION):

This arteritic type is the less common form of ischemic optic neuropathy as mentioned by ***Bajin (2008)***. Also he added that the acute ischaemia is due to inflammation of the posterior ciliary arteries and/or ophthalmic artery; it is also known as giant cell arteritis.

C. Posterior ischemic optic neuropathy:

Is a rare type of neuropathy and its diagnosis depends upon exclusion of other causes, such as stroke and brain tumor. It is represented by Decreased visual acuity and altitudinal visual field defects. The main causes of posterior ischemic optic neuropathy are Decreased blood flow in the pial capillary plexus supplying the nerve, connective tissue disorders, diabetes mellitus, trauma and radiotherapy to the orbit ***(Bajin, 2008)***.

Other causes of optic neuropathy:

2) Toxic Optic neuropathy:

The causes of such disorder are variable. A lot of agents e.g; Chloramphenicol, Ethambutol and Amiodarone may cause toxic optic neuropathy; alcohol and tobacco have also a greater risk of causing toxic neuropathy ***(Osborne and Balcer, 2013).***

3) Inflammatory optic neuropathy:

The dysfunction of the optic nerve caused by inflammation is called optic neuritis. ***Foroozan et al. (2003)*** stated that the acute demyelinating optic neuropathy is the most common type of inflammatory optic neuritis.

4) Traumatic Optic Neuropathy (TON):

TON refers to the direct or indirect affection of optic nerve secondary to trauma ***(Steinsapir and Goldberg, 2011).***

AIM OF THE WORK

This work aims at demonstrating histological changes induced by application of sildenafil citrate on adult and senile optic nerve of albino rats by using microscopic examination and immunohistochemisty.

ANATOMY, HISTOLOGY AND EMBRYOLOGY OF OPTIC NERVE IN HUMAN

The optic nerve consists of the axons of the ganglion cells of the retina. The nerve begins from optic disc, extends to optic chiasma where the two nerves meet. The nerve fibers originate from the nasal half of each retina decussate, while the nerve fibers coming from temporal side of the retina continue without crossing fig.(1) ***(Smith and Strottmann, 2001).***

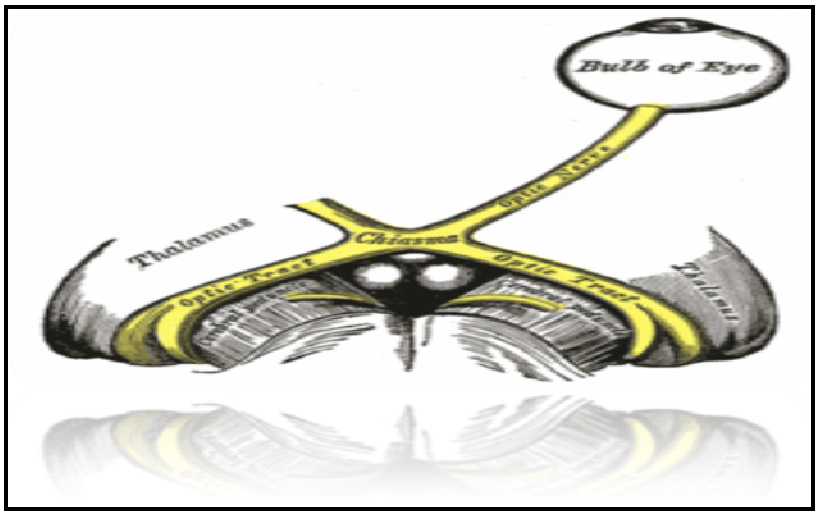

Figure (1): Anatomical pathway of optic nerve ***(Smith and Strottmann, 2001)***.

From this point, the nerve fibers form optic tract that terminate in the lateral geniculate body, while few other axons terminate in the pretectal nucleus which is responsible for pupillary light reflex. In its course from the lateral geniculate nucleus to the striate cortex, optic radiation crosses the

retrolentiform part of internal capsule. Some of the optic radiation axons run out into the temporal lobe called Meyer's loop ***(Smith and Strottmann, 2001).***

Parts of optic nerve:

The total length of optic nerve is ranging from40-45 mm, it consists of four parts **Intraoccular part**:- 1 mm, **Intraorbital part**:- 25 mm, **Intracanalicular part** 6-9mm and at last the **intracranial cranial** 10 mm.

Intra occular part:

1mm in length, the nerve fibers forming the optic nerve exit from the eye posteriorly through a hole in the sclera that is closed by a mesh-like structure called the lamina cribrosa, formed by a multilayered network of collagen fibers which is related to the sclera ***(Radius and* Gonzales*, 1981)***.

Intraorbital part:

It is 25mm in length extends from back of eyeball to optic foramen. The straight line distance from back of the globe to optic canal is much less, with relative excess of the optic nerve length being necessary for free movement of globe during eye movement ***(Bron et al., 1997)***.

Intracanalicular part:

It is 6 to 9 mm in length. This part it is closely related to ophthalmic artery inferolaterally ***(Duke and Wybar, 1961)***.

Intracranial part:

It is 10 mm in length, this part is found above the cavernous sinus; converge with the fellow nerve over diaphragma sellae to form optic chiasma ***(Bron et al., 1997)***.

Hoyt and Luis (1962) stated that the last three parts of the optic nerve are composed of myelinated axons; neuroglial cells, including astrocytes, microglia, and oligodendrocytes; and fibro vascular septa.

Histology of optic nerve:

In cross-section using Hematoxylin and Eosin (H&E) stain, the principal myelinated optic nerve fibers appear as small, faintly stained, eosinophilic dots surrounded by relatively clear halos ***(Cowey and Stoerig, 1991)*** and these clear halos, representing dissolution of the lipid myelin sheath**.**

Under electron microscopy ***Cowey and Stoerig (1991)*** stated that the nerve fibers are identified as cytoplasm with mitochondria enveloped by multilaminar myelin sheaths.

Morin (1994) described the specific arrangement of the axons of optic nerve: stating that the peripheral retinal axons are located in the peripheral portion of the optic nerve, and the central area of the nerve contains posterior retinal axons.

He added that macular fibers coming form the papillomacular bundle enter the disc temporally; they remain temporal for a short distance behind the eye, but as they proceed further posteriorly these fibers become diffusely distributed.

Histology of optic nerve head:

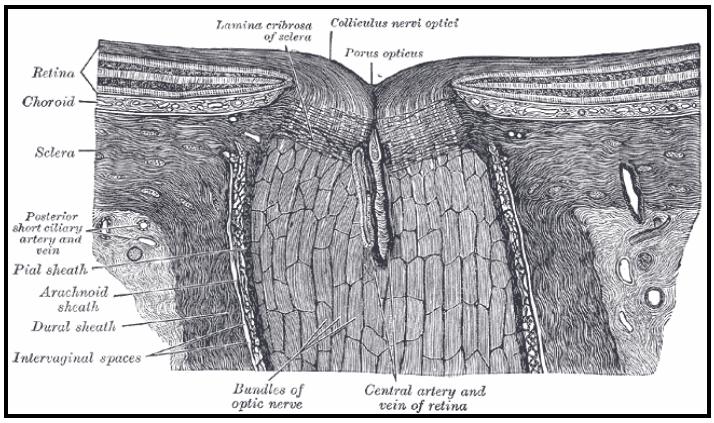

Figure (2): Histology of optic nerve head ***(Hayreh, 1974).***

The optic nerve head extends from the surface of the optic disc to the posterior scleral surface, where the axons of the retinal ganglion cells form bundles that emerge from the nerve fiber layer and turn to exit from the globe. The optic nerve head is divided into three regions: the surface nerve fiber layer, the prelaminar region, and the lamina cribrosa region fig.(2) ***(Hayreh, 1974).***

1- The surface nerve fiber layer contains compact optic nerve fibers which is covered by a layer of astrocytes (the inner limiting membrane of Elschnig) ***(Hernandez et al., 1986).***

2-The prelaminar region consists of nonmyelinated axons, astrocytes, capillaries, and surrounding connective tissues. The axons are arranged in bundles and surrounded by astrocytes ***(Hayreh, 1974).***

3-The lamina cribrosa is a specialized, sieve-like region with multiple oval or rounded openings through which pass the nerve fibers and the central retinal vessels. This region consists of dense and compact collagenous sheets of scleral trabecular alternating with glial sheets. The astrocytes that line the openings in the lamina cribrosa form a continuous glial membrane that surrounds each nerve fiber bundle and separates the nerve fiber bundles from the adjacent connective tissue fig.(3) ***(Hernandez et al., 1986).***

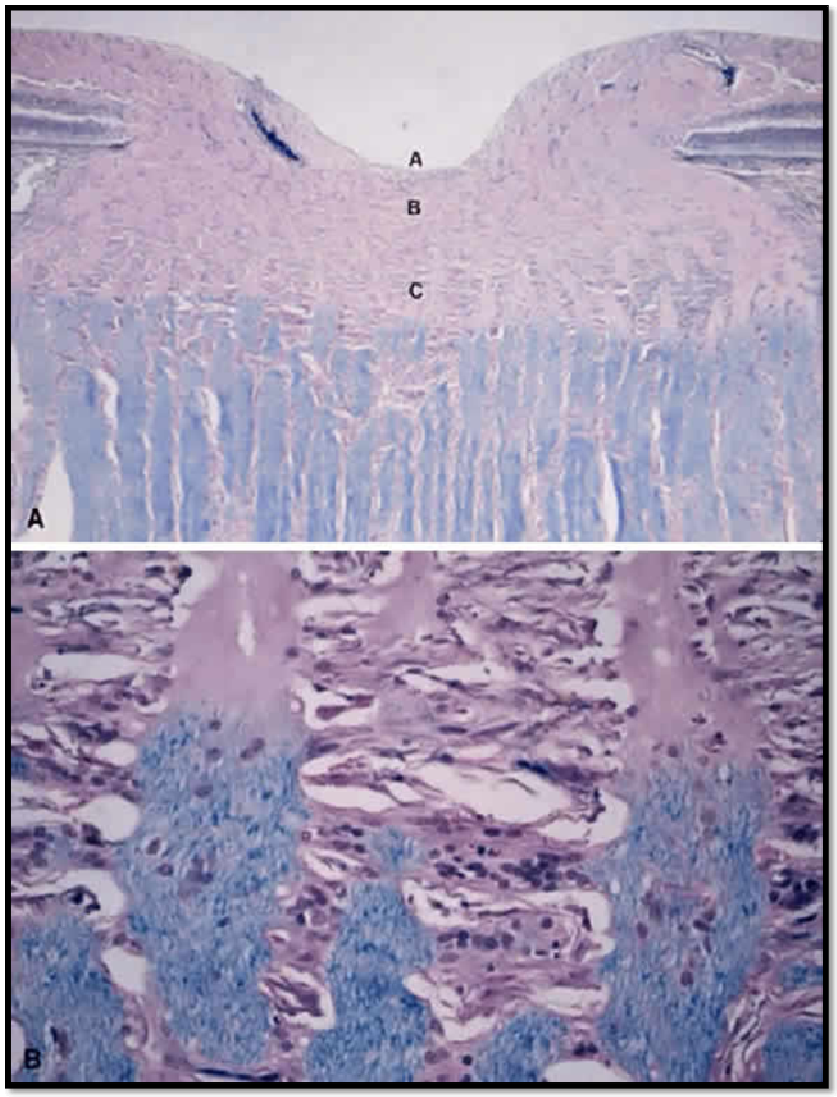

Figure (3): A. Histology of the optic nerve head. Longitudinal section: (*A*) the surface nerve fiber layer and the physiologic cup. (*B*) Prelaminar region. (*C*) Lamina cribrosa region. The nonmyelinated axons in the optic nerve head are not stained by Luxol fast blue, whereas the myelinated axons behind the lamina cribrosa are stained. Luxol fast blue, × 40. **B.** High magnification demonstrates the transmission of the nonmyelinated and myelinated axons, × 400***(Hernandez et al., 1986)*.**.

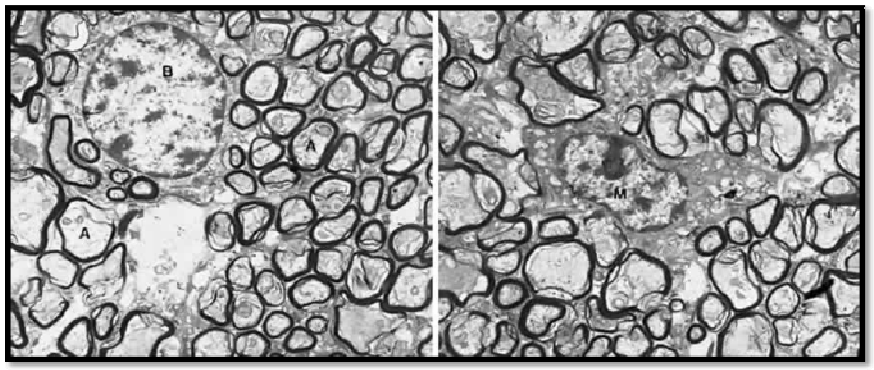

Figure (4): Ultrastructure of the optic nerve. (*A*) Axons are surrounded by myelinated sheath. (*B*) Oligodendritic cell. (*M*) Microglial cell. × 18,750 ***(Lampert et al., 1968***).

Glial cells:

Sturrock (1984) mentioned that the glial component of the optic nerve as in the central nervous system include astrocytes, oligodendrocytes, are derived from neuroectoderm. While there is acontroversy about the origin of microglia whether from mesoderm rather than ectoderm.

Histological study by ***Ling and Wong (1993)*** using H&E demonstrated that all the astrocytes in the optic nerve and optic nerve head appear to be fibrous, with a large cell body and many long, coarse processes; adding that they line the borders between axons and other tissues of the area.

Functionally, astrocytes provide scaffolding that supports the axons and maintains a stable biochemical environment around the nerve fibers ***(Miller and Raff, 1984)***. They added that at the site of axonal loss, astrocytes can form scar tissue, known as gliosis.

Under electron microscopy ***Raff (1989)*** found that the astrocytes are characterized by rich processes, extensively lobulated nuclei, numerous intermediate glial filaments, glycogen granules and a wide type of granular endoplasmic reticulum.

Oligodendrocytes show small, rounded or oval nuclei, a granular cytoplasm, and delicate branching processes that terminate in loops**,** and they located in groups, near the center of the axonal bundles as stated by ***Skoff et al. (1986)*** Adding that they can make and maintain myelin sheaths of the axons, similar to the function of Schwann cells in the peripheral nerves, but without forming a basement membrane around the myelin sheaths**.**

Electron microscopy studies by ***Lampert et al. (1968***) described oligodendrocytes as moderately electron dense compared with astrocytes. The nucleus is rounded or oval and is usually eccentrically located; leaving a large mass of cytoplasm at one pole of the cell. He added that the cytoplasm is rich in ribosomes, either free or associated with the endoplasmic reticulum. The Golgi complex is well developed fig.(4).

Microglia cells are irregularly oval, containing small nuclei and many long and slender branching processes ***(Penfold et al., 1993).*** In the normal optic nerve, these cells are ordinarily present in small numbers, and most are found within

bundles of axons, with some situated adjacent to the glial septa and to blood vessels.

Under electron microscopy, microglial cells have small, heterochromatic nuclei. The cytoplasm shows vacuoles, granular endoplasmic reticulum arranged in long, narrow strands, and various inclusions, including large dense bodies, lamellar bodies, myelin bodies ***(Penfold et al., 1993***).

Meningeal coverings of optic nerve:

The Intraorbital portion of the optic nerve is enclosed inside three sheaths that are continuous with the meninges of the central nervous system: Dura mater, Arachnoid, and Pia mater. The outermost of these is the dura mater, which is a dense collagenous and elastic tissue ***(Ling and Wong, 1993).***

Hoyt and Luis (1962) stated that the dura mater anteriorly, frays and inserted into the sclera and the sheaths of recti muscles along with the ciliary arteries and nerves; while posteriorly it fuses with the perioesteum of the bony canal and with annulus of zinn at the apex of the orbit.

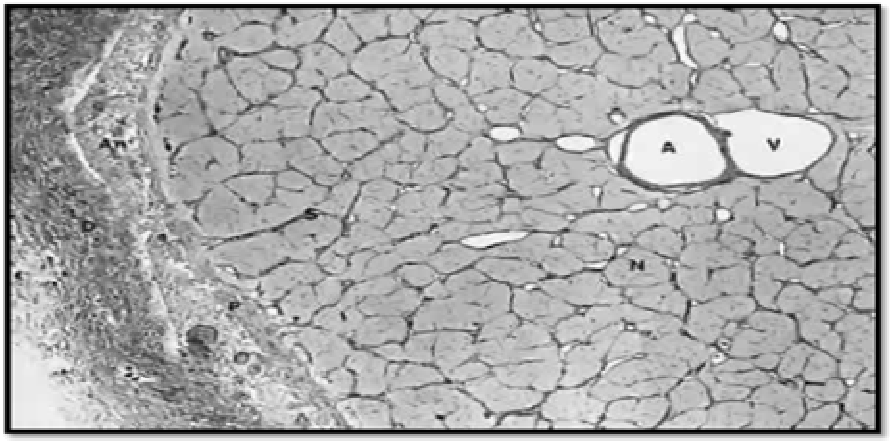

Figure (5): Cross-section of the optic nerve. (*A*) central retinal artery; (*V*) central retinal vein; (*S*) connective septa from the pia mater; (*P*) pia mater; (*An*) arachnoid cell nests; (*D*) dura mater; (*N*) axon bundles intermingled with glia cell nuclei ***(Miller and Raff, 1984).***

Wolter (1995) described the arachnoid as being composed of trabeculae of collagenous and elastic fibers lined by meningothelia. It contains numerous vessels, along with some fibroblasts and histiocytes**.**

The pia mater lies tightly on the surface of the nerve and consists of collagenous fibers, elastic fibers, and a fused glial layer. The pia mater surrounds the nerve and sends fibers into the substance of the nerve to form the characteristic septa. The septa are separated from the surrounding nervous tissue by the foot processes of the astrocytes fig.(5) ***(Miller and Raff, 1984).***

Wolter (1995) added that the pia mater is connected to the sclera and choroid anteriorly, while posteriorly, it continues to form the single sheath around the intracranial portion of the optic nerve through the optic foramen**.**