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ORIGINAL ARTICLE

Changes induces by haloperidol (antidepressant drug) on the developing retina of the chick embryo

Badria Fathy Abd-Elmagid, Fawzyah Abdullah Al-Ghamdi *

Department of Zoology (Embryology), Girls College of Education in Jeddah, King Abdul-Aziz University, Saudi Arabia

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KEYWORDS

Retina;
Haloperidol;
Toxicity;
Retardation;
Degeneration;
Chick embryo

Abstract Morphological and histological studies were done on the retina of chick embryos of 6th, 10th and 16th days of incubation by a single dose of haloperidol (0.25 mg/egg), injected on day zero and 5 of incubation. To get an idea about the extent of the teratogenic effect of this drug on the development retina. Sign of malformation in the chick embryo after administration of haloperidol were seen as absent of the ear vesicles, eyes or decreased size of them. Retardation of growth of the retina at 6th, 10th and 16th days treated chick embryo were observed as evidenced of reduction of the size of the retina, associated with sign of degeneration of the retina cells.

Conclusion: The injection of haloperidol drug give rise to several side effects as retardation of growth and degeneration of the cells. The decrease of the thickness of the layers and less density of the cells was related to direct effect of the drug on the cells of this organ. Also on the DNA formation and on the retardation of cellular mitotic activates, therefore the retina appeared decrease in thickness and less cell density with degeneration its cells.

1. Introduction

Because of the diversity of the structure and the active biochemical processes that take place both independently of, and in conjunction with the systemic metabolism, the eye is second to the liver in showing the manifestations of the drug toxicity. The antipsychotic drugs are classical into several groups, these groups include butyrophenone derivatives which contain haloperidol, haloperidol is the most widely used drug in this group (Potter and Hollister, 2001; Tierney et al., 2002).

The neuroleptic drug (haloperidol) was selected for the present study mainly due to its effects as a relatively small and localized population of the cell with a well-known transmitter chemistry. The previous studies have reported a marked reduction in the [3H] thymidine incorporation in brain after acute administration of high doses of haloperidol (Patel et al., 1981; Backhouse et al., 1982; Patel and Lewis, 1988). The haloperidol blocked of DNA polymerases and decreased cell proliferation in brain (Castro et al., 1990). Some authors showed that the prenatal administration of D_2-selective drugs such as haloperidol produced a postnatal decrease in the number of striate D_2 receptors (Rosengarten et al., 1983; Miller and

* Corresponding author.
E-mail address: dr_fawzyah1@hotmail.com (F.A. Al-Ghamdi).

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Friedhoff, 1988). Prenatal HAL treatment has been reported to decrease the number of postsynaptic DA receptors (Scalzo et al., 1989). The prenatal administration of haloperidol produced reliable stunting of body and brain weight of the offspring (Williams et al., 1992). The metabolite of haloperidol induced apoptosis and DNA damage in pheochromocytome cells 12 (PC12) (Qing et al., 2003). The haloperidol can affect DNA methylation states in the brain, as well as in certain other tissues, and raise the possibility of antipsychotic drugs to play a role in the observed disparity in methyl cytosine (mC) (Shimabukuro et al., 2006).

The present study was done to determine the effect of haloperidol on the developing retina of the chick embryo.

2. Material and methods

Hundred fertile eggs were used in this work. They were incubated at 37 °C in a thermostatically controlled electric incubator under good ventilation and proper humidity (60%). The eggs were divided into two groups. The first group composed of (20 eggs) and was used as a control for studying normal development and structure of the retina. The eggs of the second group (80 eggs) were injecting by a dose of haloperidol equivalent to human therapeutic dose (0.25 mg/egg) in the air sac space. This group was subdivided into 2-subdivision according to time of injection; (1) subdivision (**T0**) injection at zero-day before incubation by (single therapeutic dose); while the (2) subdivision (**T1**) injection at the first week at the 5-the of incubation by one dose.

The control group of the fertilized chick eggs were injection by Sesame oil at the same days of the two treated subgroup by haloperidol drug at the air chamber (air-sac) (Allam et al., 1976). All eggs were opened at the selection day of study (6, 10 and 16-days).

All the embryo were extracted and the heads with the two eyes were fixed in Bouin's solution for 3–5 days, then the steps of preparation for studying histological structure of chicken embryo (dehydrated, cleared in benzene, embedded in soft paraffin wax and cut at 8-μm thickness then stained by Haematoxylin and eosin (to examined general structure), Holmes silver stain (to studies and compare the amount of the fibers) (Drury and Wallington, 1980).

3. Result

In this investigation the normal development of retina was studied and comparing with the effect of haloperidol drug on histological changes induced on the structures of retina.

Morphological changes in the developing embryos were observed at the 6-and 10-days of incubation as absent the ear vesicles and the eyes or decreased the size of them, severe abdominal hernia, congesting the body, decreased the length of the body and other changes (Fig. 1A and B).

3.1. Morphogenesis and histogenesis of the retina of the chick embryos

3.1.1. Sixth days chick embryo

3.1.1.1. The retina of sixth days control chick embryo. In the present study, the retina was composed of 3-layers from outwards inwards; pigmented layer; sensory (neuroblastic) zone and marginal layer, the development was rapidly extended from the posterior part to the anterior part of the retina (Fig. 2).

A layer of pigmented epithelium (PE): it was formed of a single layer of cubical cells with basally located oval or rounded deeply-stained nuclei, the Neuroblastic zone (NZ): this layer was the thickest one (compose of 10 layers), it was formed of several strata of crowded cells with deeply-stained oval or round nuclei (Fig. 3).

3.1.1.2. The retina of sixth-days treated chick embryo. Several sign was observed as retardation of growth and degeneration of cells were seen as the effect induced by the drug in relation to the time of injection.

The retina of sixth-days (T0) treated chick embryo: The examination of the horizontal sections of the retina of the six-days old chick embryo injected on the 0th day of incubation by a dose of haloperidol equivalent to the human therapeutic dose (0.25 mg/egg) showed marked retardation of growth of retina as evidenced by marked thinning in all layers of the retina (Figs. 4 and 5). The layers of the retina were reduced to 7–8-layers cell thick (Fig. 5) as compared with the 10-layers cell thick of the control one (Fig. 3). The appearance of cavities, less mitotic figures in the basal layer of (neuroplas-

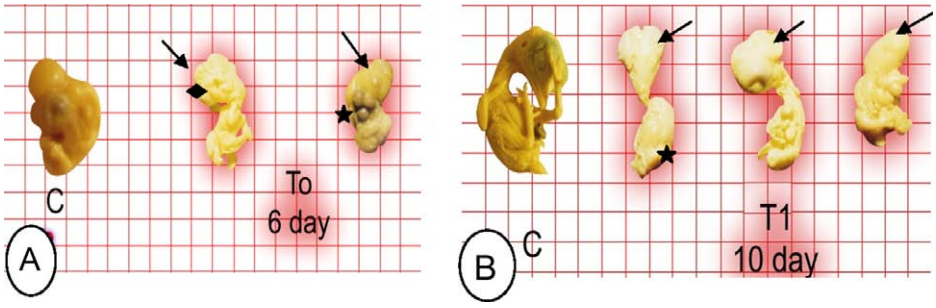

Figure 1 (A) Showing the malformation in the treated chick embryo comparing with the control one. Notice in treated chick embryo (T0) of 6-days; absent the eyes ↑, hernia, Congesting the body, decreased the length of the body, absent the lower limbs in one of the chick and irregularly shapes in another (★). (B) Showing the malformation in the treated chick embryo comparing with the control one. Notice in treated chick embryo (T1) of 10-days; sever hernia (★), congesting the body, decreased the length of the body, irregularly shapes of the limbs or absent completely , absent the ear vesicles and the eyes or decreased the size of them ↑, the feather not formed, smaller the beak (rostrum) (♦), and kinking of the neck.

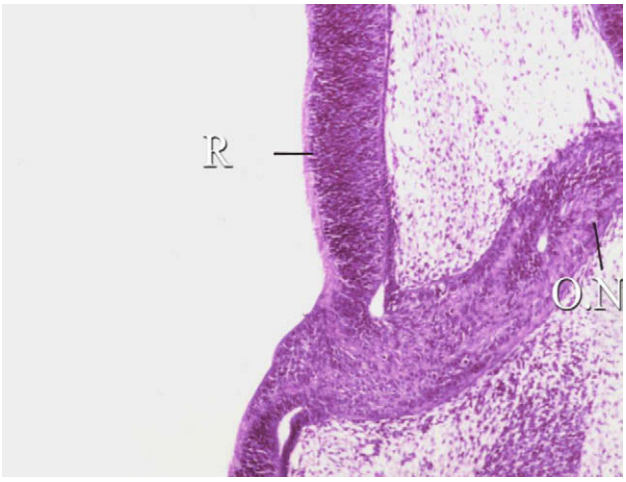

Figure 2 A horizontal section of the retina of 6-days old control chick embryo showing retina (R) and optic nerve (ON) (Hx and E × 100).

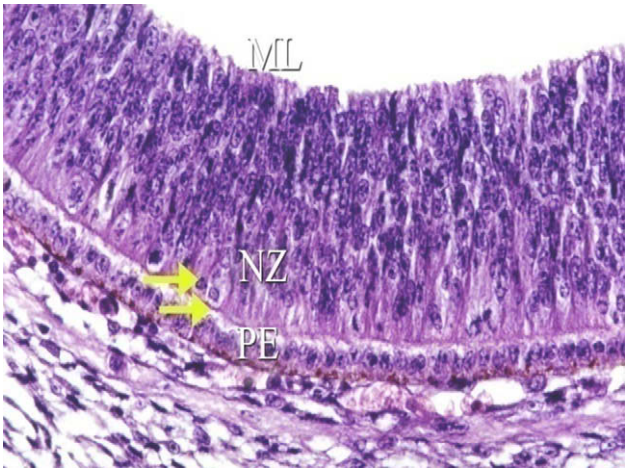

Figure 3 The part of (Fig. 2) magnified to show the pigmented epithelium (PE), neuroplastic zone (NZ) which formed of (9–10) layers cell thick, with the mitotic figures (↑↑) at the first layer of this and marginal layer (ML) (Hx and E × 400).

tic cells), the marginal layer of the retina was hardly seen (Fig. 5).

The retina of sixth-days (T1) treated chick embryo: The retina consist of 3-layers (Fig. 6) as the control one, but the layers of the retina were reduced to 7–8-layers cell thick so it was less crowded (Fig. 7) as compared with the 10-layers cell thick of the control one (Fig. 3), cavities and empty spaces were seen, pyknotic nucleus were appeared in the neuroplastic zone zero.

3.1.2. Tenth days chick embryo

3.1.2.1. The retina of 10-days control chick embryo. As age advanced; the examination of the horizontal sections of retina of 10-days old control chick embryo showed that the retina was increase in thickness and more developed and consists of two layers; outer pigmented layer and inner sensory layer; from out wards in wards (Fig. 8). The layer of pigmented epithelium was formed of cuboidal cell with basal oval or rounded deeply-stained nuclei; the sensory layer were formed of 8-layers as follows:

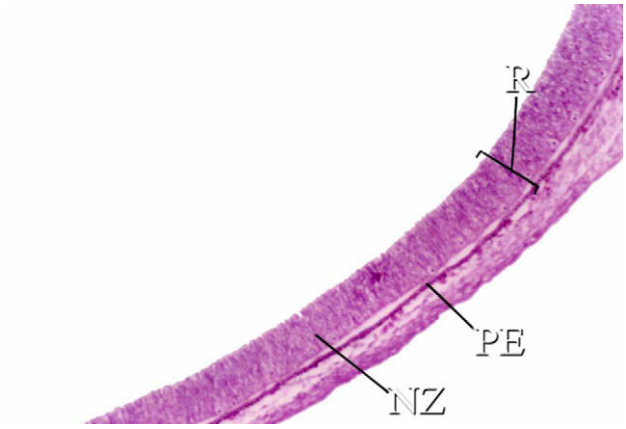

Figure 4 A horizontal section of the retina of 6-days old treated (T0) chick embryo showing retina (R) consists of pigmented layer (PE) and neuroplastic zone (NZ). Note that its less thick than that of control one (Hx and E × 100).

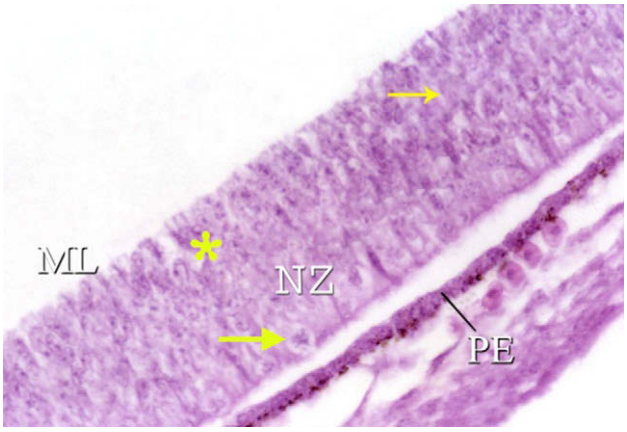

Figure 5 The part of (Fig. 4) magnified to show the pigmented epithelium (PE), neuroplastic zone (NZ) which formed of (7–8) layers cell thick of less crowded cells, many small cavities (★) appeared in the neuroplastic and some cell appeared swellings (↑) and marginal layer (ML) (Hx and E × 400).

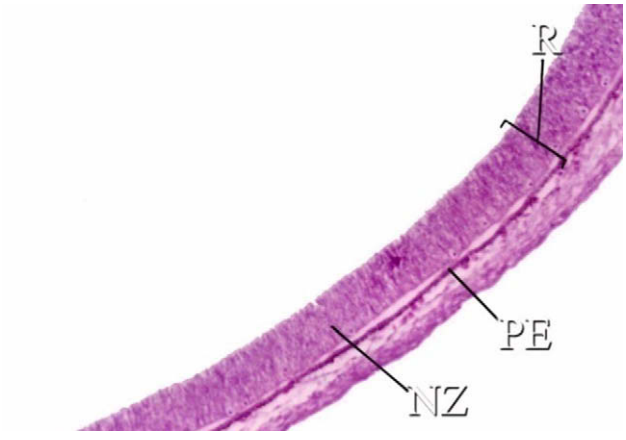

Figure 6 A horizontal section of the retina of 6-days old treated (T1) chick embryo showing retina (R) consists of pigmented layer (PE) neuroplastic zone (NZ) (Hx and E × 100).

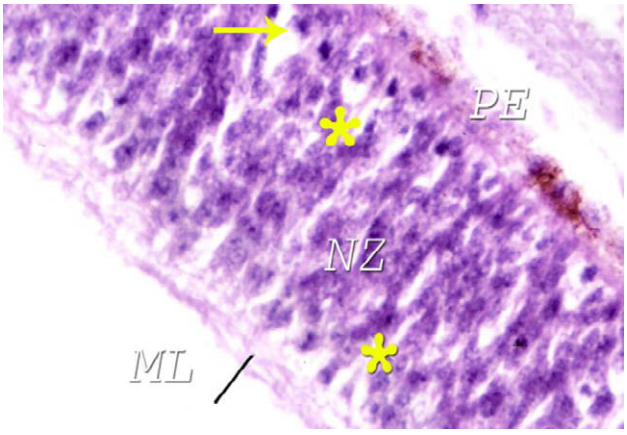

Figure 7 The part of (Fig. 6) magnified to show the pigmented epithelium (PE), neuroplastic zone (NZ) which formed of (8–9) layers cell thick of less crowded cells, cavities and empty spaces (★) with pyknotic cells (↑) in them and marginal layer (ML) (Hx and E X400).

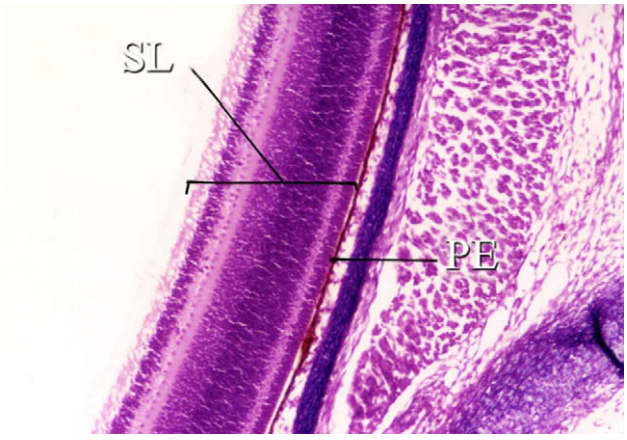

Figure 8 A horizontal section of the retina of 10-days old control chick embryo showing that the retina (R).consists of two layers; outer pigmented layer (PE), and inner sensory layer (SL) (Hx and E × 100).

1. External limiting membrane (ELM).
2. The layer of the rods and cons (R & C), this layer was the outer layer of the neuroblastic zone which was differentiated into rods and cones (visual cells), these cells appeared small and has spherical or rounded deeply nuclei.
3. Henle's membrane (HM), this membrane was only differenced in the avian retina and formed of the fibers of the previous layer.
4. Inner nuclear layer (INL) formed of (15–17) layers cell thick, and it differentiated to 3-sublayers; inner horizontal cells (amacrine cells) and intermediate horizontal cells (bipolar cells) and outer horizontal cells.
5. Inner reticular layer (IRL). This nerve fibers layer which was associated with few small cells at the outer surface of it.
6. The ganglion cells layer (GCL). This layer was appeared to be arranged in (4–5) strata of loosely-arranged cells with oval or rounded deeply – stained nuclei and faint cytoplasm.

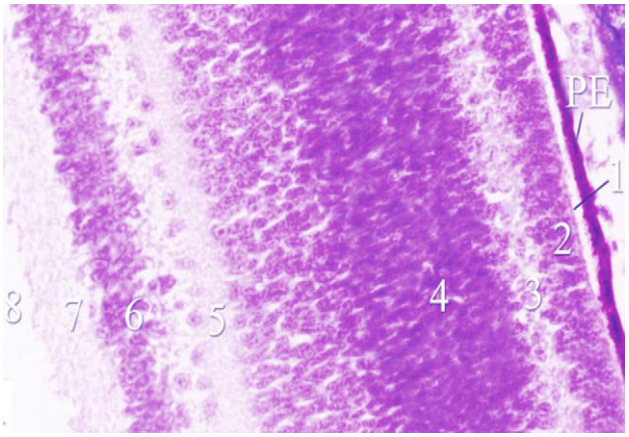

Figure 9 The part of (Fig. 8) magnified to show the retina consists of two layers; outer pigmented layer and inner sensory layer which is formed of 8-layers. External limiting membrane (ELM) layer of rods and cons (R&C). Henle's membrane (HM). Inner nuclear layer (INL) formed of (15–17) layers cell thick, and it formed of 3-sub groups of cells. Inner reticular layer (IRL). Ganglion cells layer (GCL) formed of (4–5) layers cell thick. Nerve fibers layer (NFL). Internal limiting membrane (ILM) (Hx and E × 400).

7. The nerve fibers layer (NFL). This layer was non-cellular layer, and formed of the processes of cells of ganglion cell layer.
8. Internal limiting membrane (ILM). It was formed of the inner-most layer of the retina. In haematoxylin and eosin stain, it appeared as a thick lightly-stained line (Fig. 9).

3.1.3. The retina of 10th-day treated chick embryo

3.1.3.1. The retina of 10th-day (T0) treated chick embryo. The examination of the horizontal sections of the retina of the 10-days chick embryo treated on the 0th day of incubation by a single dose of haloperidol (0.25 mg/egg) showed that the retina (R), consists of two layer; outer pigmented layer, and inner sensory layer (Fig. 10). Note that the retina is less thick than that of the control one (Fig. 8) of the same age.

Marked retardation of the growth of the retina was seen (Fig. 11) as evidenced by; the layer of rods and cons has less condensed cells with many spaces between the cells, and note few cytoplasmic processes penetrated on the outer limiting membrane. The Inner nuclear layer was reduced to be formed of (11–12) layers cell thick, as compared with the control one of the same age which was formed of (15–17) layers cell thick (Fig. 9). Many cavities appeared between the cells, this layer was hardly differentiated into its 3-sub group. Some pyknotic and degenerated cells has been appeared in this layer. Five-inner reticular layer has very few widely dispersed fibers. Also the ganglion cells layer became markedly-reduced as it was composed of (1–2) layers of loosely packed cells, as compared with the control one of the same age which was composed of (4–5) layers cell thick (Fig. 9). The Internal limiting membrane appeared irregular, interrupted or hardly seen in some parts of the retina (Fig. 11).

3.1.3.2. The retina of 10th-day (T1) treated chick embryo. The examination of the horizontal sections of the retina of the 10-

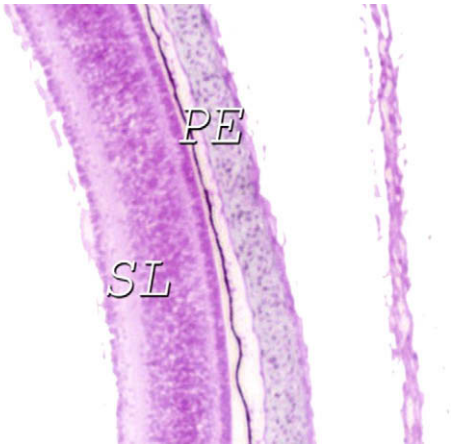

Figure 10 A horizontal section of the retina of 10-days old treated (T0) chick embryo showing that the retina (R) consists of two layer; outer pigmented layer (PE), and inner sensory layer (SL). Note the retina is less thick than of the control one (Hx and E × 100).

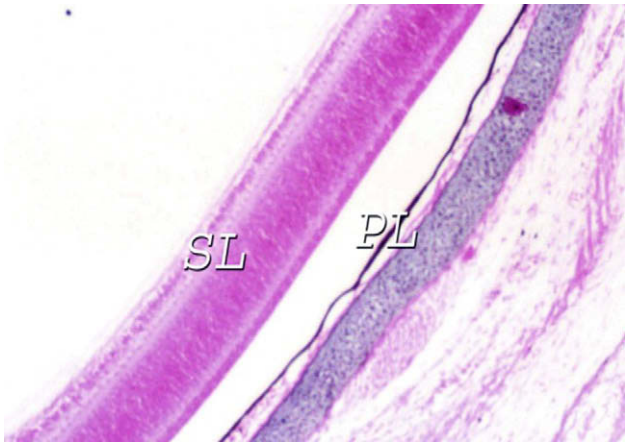

Figure 12 A horizontal section of the retina of 10-days old treated (T0) chick embryo showing that the retina (R) consists of two layer; outer pigmented layer (PE), and inner sensory layer (SL). Note the retina is less thick than of the control one (Hx and E X100).

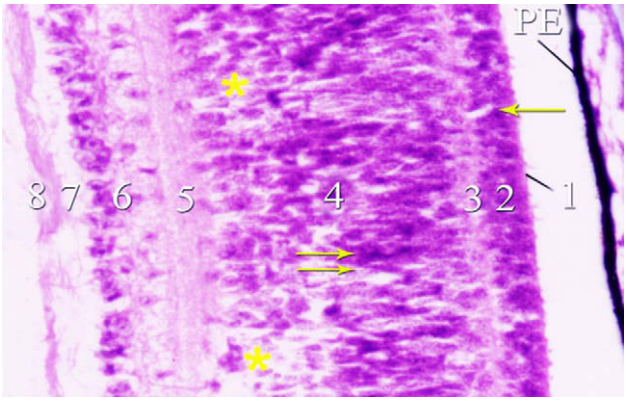

Figure 11 The part of (Fig. 10) magnified to show the pigmented layer (PE) and the sensory layer (SL) which is formed of 8-layers. Note that in the 2-layer of rods and cons (R&C) has less condensed cells with many spaces between the cells (↗), and note few cytoplasmic processes penetrated on the outer limiting membrane. The 4-Inner nuclear layer (INL) which formed of (11–12) layers cell thick with many cavities (★) between the cells, this layer hardly differentiated into its 3-sub group, and there are some pyknotic and degenerated cells (↗↗). Five-Inner reticular layer (IRL) has very few widely dispersed fibers. Also the 6-Ganglion cells layer (GCL) formed of (1–2) layer of loosely packed cells (Hx and E × 400).

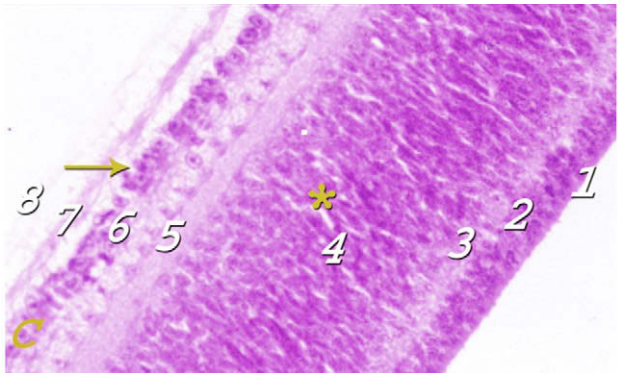

Figure 13 The part of (Fig. 12) magnified to show the sensory layer (SL) of the retina which is formed of 8-layers. Note the 4-Inner nuclear layer (INL) it formed of (11–12) layers cell thick , and hardly differentiated into 3-sub groups , and contain some small cavities (★) and the 6-Ganglion cells layer (GCL) it formed of (1–2) layers cell thick with pyknotic cells (↗) (Hx and E X400).

day chick embryo treated on the 5th day of incubation by the same dose of haloperidol showed the retina consists of two layer; outer pigmented layer, and inner sensory layer (Fig. 12). But the retina is less thick than that of the control one (Fig. 8). Marked retardation in the growth and degeneration in the cells (Fig. 13); as evidenced by; the Inner nuclear layer it formed of (11–12) layers cell thick; compared with the control one of the same age (Fig. 9), and hardly differentiated into its 3-sub groups. Some small cavities appeared through this layer .The ganglion cells layer was formed of (1–2) layers cell thick with some pyknotic nuclei seen as compared with the control one of the same age which was composed of (4–5) layers cell thick. The Internal limiting membrane appeared irregular and less thick (Fig. 9).

3.1.4. Sixteen days chick embryo

3.1.4.1. The retina of 16-days old control chick embryo. The examination of horizontal sections of retina of 16-days control chick embryo showed that the retina formed of two layers: outer pigmented layer (PE) and inner sensory layer (SL) (Fig. 14), the retina appeared full developed, and it was decreased in the thick as the nuclear layer and ganglion layer was normally reduced in thick, beside the increased of the fibrotic layers (Inner reticular layer and Nerve fiber layer) (Fig. 15) and (Fig. 20A). The sensory layer (SL) was formed of 8-layers as the previous age (10-days):

1. External limiting membrane (ELM).
2. Layer of rods and cons (R & C) {visual cells}.
3. Henle's membrane (HM).

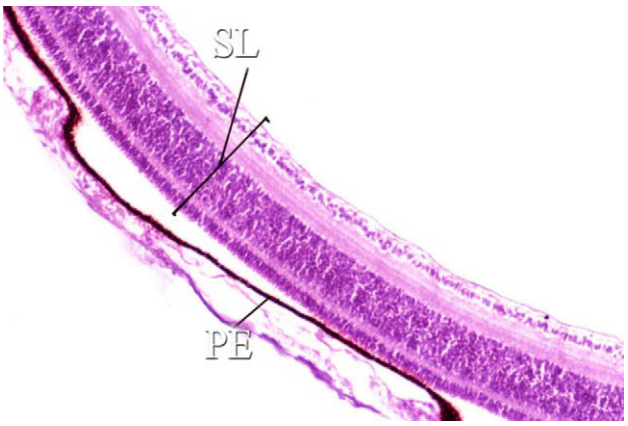

Figure 14 A horizontal section of the retina of 16-days old control chick embryo, showing retina (R) formed of two layer: outer pigmented layer (PE) and inner sensory layer (SL) (Hx and E × 100).

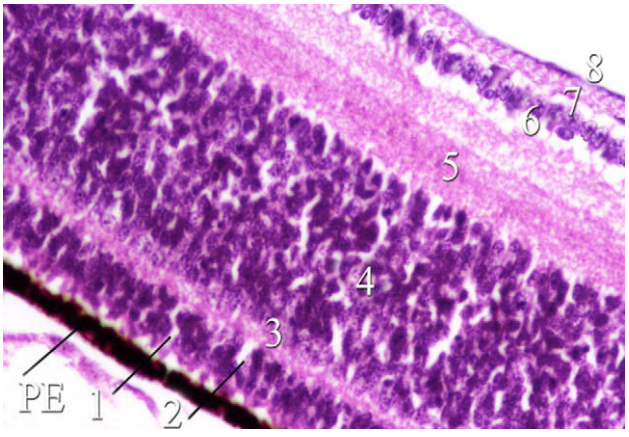

Figure 15 The part of (Fig. 14) magnified to show the outer pigmented layer (PE) and inner sensory layer (SL) which formed of 8-layers: 1-external limiting membrane (ELM). Two-layer of rods and cons (R&C) {visual cells}. 3-Henle's membrane (HM). Four-inner nuclear layer (INL) formed of (10–11) layers cell thick. Five-Inner reticular layer (IRL) formed of nerve fiber. Six-Ganglion cells layer (GCL) reduced to be formed of (1–2) layers cell thick. Seven-nerve fibers layer (NFL). Eight-internal limiting membrane (ILM) (Hx and E × 400).

4. Inner nuclear layer (INL) which was formed of (10–11) layers cell thick, as compare with the 10-day which was composed of (15–17) layers cell thick (Fig. 9).
5. The Inner reticular layer (IRL) formed of thick nerve fiber, compare with the 10-days (Fig. 9).
6. The Ganglion cells layer (GCL) reduced to be formed of (1–2) layers cell thick, as compare with the 10-days, which was composed of (4–5) layers cell thick (Fig. 9).
7. Nerve fibers layer (NFL).
8. Internal limiting membrane (ILM).

3.1.4.2. The retina of 16-days old treated chick embryo. The examination of horizontal section of the retina of 16-days old chick embryo which treated by therapeutic single dose of the haloperidol drug which equivalent to (0.25 mg/egg). Showed that the retina was decreased in size and retardated in growth. The rods and cons appeared with irregular cytoplasmic processes. The inner nuclear layer and ganglion layer also affected as the numbers of the layer cells thickness is reduced with sever degeneration had been occurred, while the nerves fibers layers was also affected.

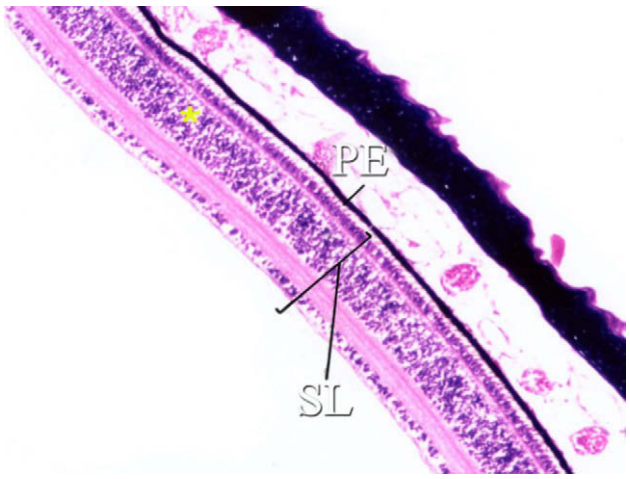

Figure 16 A horizontal section of the retina of 16-days old treated (T0) chick embryo, showing retina (R) formed of two layers: outer pigmented layer (PE) and inner sensory layer (SL) which is formed of less crowded cells. Note many cavities appeared between the cell and layers (★) (Hx and E X100).

3.1.4.3. The retina of 16-days old (T0) treated chick embryo. The examination of horizontal section of the retina of 16-days old (T0) treated chick embryo, showed that the retina formed of pigmented layer and inner sensory layer; which is formed of less crowded cells with many cavities (Fig. 16). The layer of the rods and cons has a deformed processes. The inner nuclear layer formed of (7–8) layers cells thick as compared with the control one of the same age which was composed of (10–11) layers cell thick (Fig. 15). Many degenerated cells and cavities between the cells. Some pyknotic nuclei has been seen .The Ganglion cell layer which formed of (0–1) layer cell thick less thick as compared with the control one of the same age as it was composed of (1–2) layers cell thick (Fig. 15) .The Nerve fibers layer markedly reduced. The internal limiting membrane was interrupted and in some area was hardly seen (Figs. 17 and 20B).

3.1.4.4. The retina of 16-days old (T1) treated chick embryo. By examining of horizontal section of the retina of 16-days old (T1) treated chick embryo, showed that the retina formed of the pigmented layer and inner sensory layer which has less the crowded cells (Fig. 18), but less affected than the retina of the (T0) group (Fig. 16). The external limiting membrane penetrated by cytoplasmic process, with some pyknotic nuclei and some cavities between the layer of rods and cons. The Inner nuclear layer differentiated into two sub group and formed of (9–10) layers cells as compared with the control one of the same age which was composed of (10–11) layers cell thick (Fig. 15) with many of pyknotic nuclei and degenerated cells and many cavities between them. The ganglion cells layer

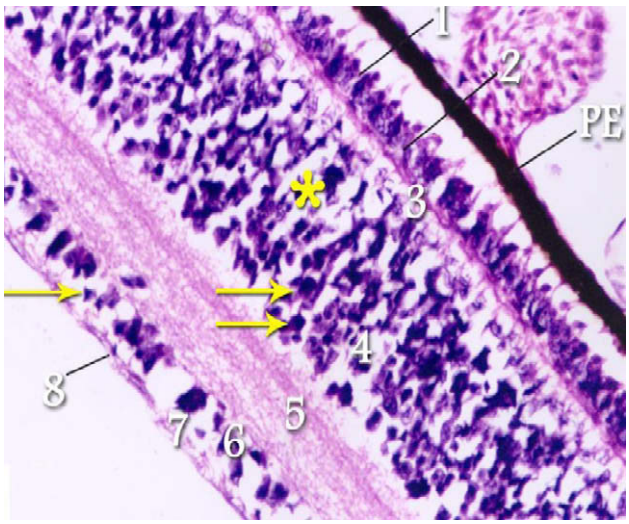

Figure 17 Part of (Fig. 16) magnified to show the pigmented layer (PE) and sensory layer (SL) which is formed of 8-layers: note the 1-external limiting membrane (ELM) penetrated by damaged cytoplasmic processes. Two-layer of rods and cons (R&C) has some pyknotic and degenerated cells. Three-(HM) faint very. Four-inner nuclear layer (INL) formed of (7–8) layers of cells, with pyknotic and degenerated cells (↗↗) and many cavities (★). Five-inner reticular layer (I.R.L) reduced in this layer. Six-Ganglion cells layer (GCL) formed of (0–1) layers cell thick of pyknotic and degenerated cells (↑) which has widely distributed cells and 7-nerve fibers layer (NFL) reduced in this layer (Hx and E × 100).

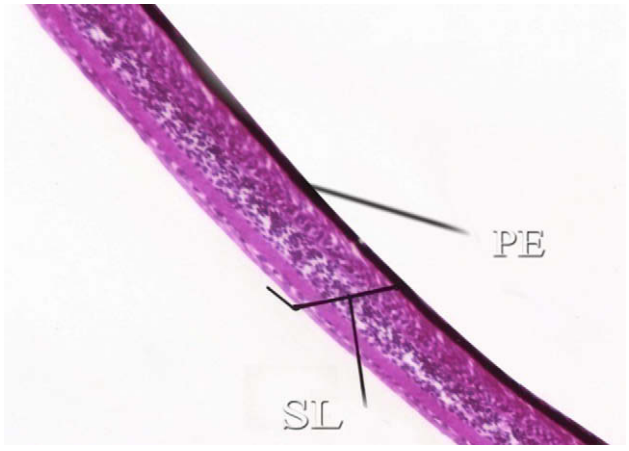

Figure 18 A horizontal section of the retina of 16-days old treated (T1) chick embryo ,showing retina (R) formed of two layers: outer pigmented layer (PE) and inner sensory layer (SL), which has less the crowded cells, but less affected than the [T0 Fig. 16] (Hx and E × 100).

which formed of (1–2) layers cell thick as compared with the control one of the same age which was composed of (1–2) layers cell thick (Fig. 15), and the interruption of the (NFL) (Figs. 19 and 20C).

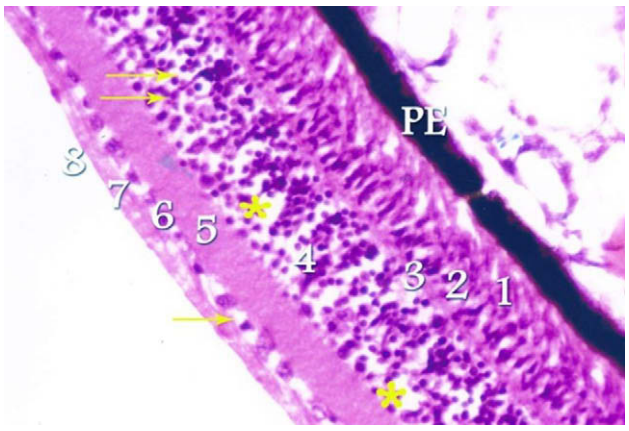

Figure 19 Part of (Fig. 18) magnified to show that the sensory layer (SL) which is formed of 8-layers: note the 2-layer of rods and cons (R&C) has deformed processes 3-(HM). Four-inner nuclear layer (INL) formed of (7–8) layers cells thick , many degenerated and pyknotic cells (↗↗) with many of cavities (★) and 6-Ganglion cells layer (GCL) formed of (0–1) layer cell thick with pyknotic and degenerated cells (↑). Seven-nerve fibers layer (NFL) markedly reduced. The 8-internal limiting membrane (ILM) interrupted and hardly seen (Hx and E × 400).

4. Dissection

In the present work, the effect of haloperidol on the retina of 6, 10 and 16-days of treated chick embryo [(T0) which injection before incubation, while (T1) injected during incubation] by a single therapeutic dose of haloperidol showed retardation of growth as evidenced by:

1. Reducing of size of the layer of the growing retina.
2. Marked thinning of some layers of the retina.
3. Changes in cells of neuroplastic and ganglionic cell layer of retina.

These effects were associated with disruption of the internal and external limiting membranes, fragmentation and necrosis of the nuclei of some cells of the ganglionic cells layer.

The dose either before or during the sensitive period of the incubation (during the first week of incubation), give rise several side effects as retardation of growth and degeneration of tissue, in the retina which selected in this study.

The findings of the present work were in agreement with findings of many workers, who reported various effects of antidepressant drug as haloperidol on the retina and other parts of body. Iqbal (1999) concluded that the safe use of antidepressants in pregnancy had not been established. There had been reports of fetal malformations, CNS effects, and developmental delay. Donohoe et al. (2006) postulated that the antipsychotics generally slowed growth and maturation, these findings suggest that antipsychotic drugs may interfere with normal developmental processes and provide a tool for investigating the key signaling pathways involved.

In the retina at all the age studied there were decreased the thickness of the layers of the retina, as the mitotic rate of cells was decreased. The rods and cons appeared with irregular cytoplasmic processes. Also the inner nuclear layer and gan-

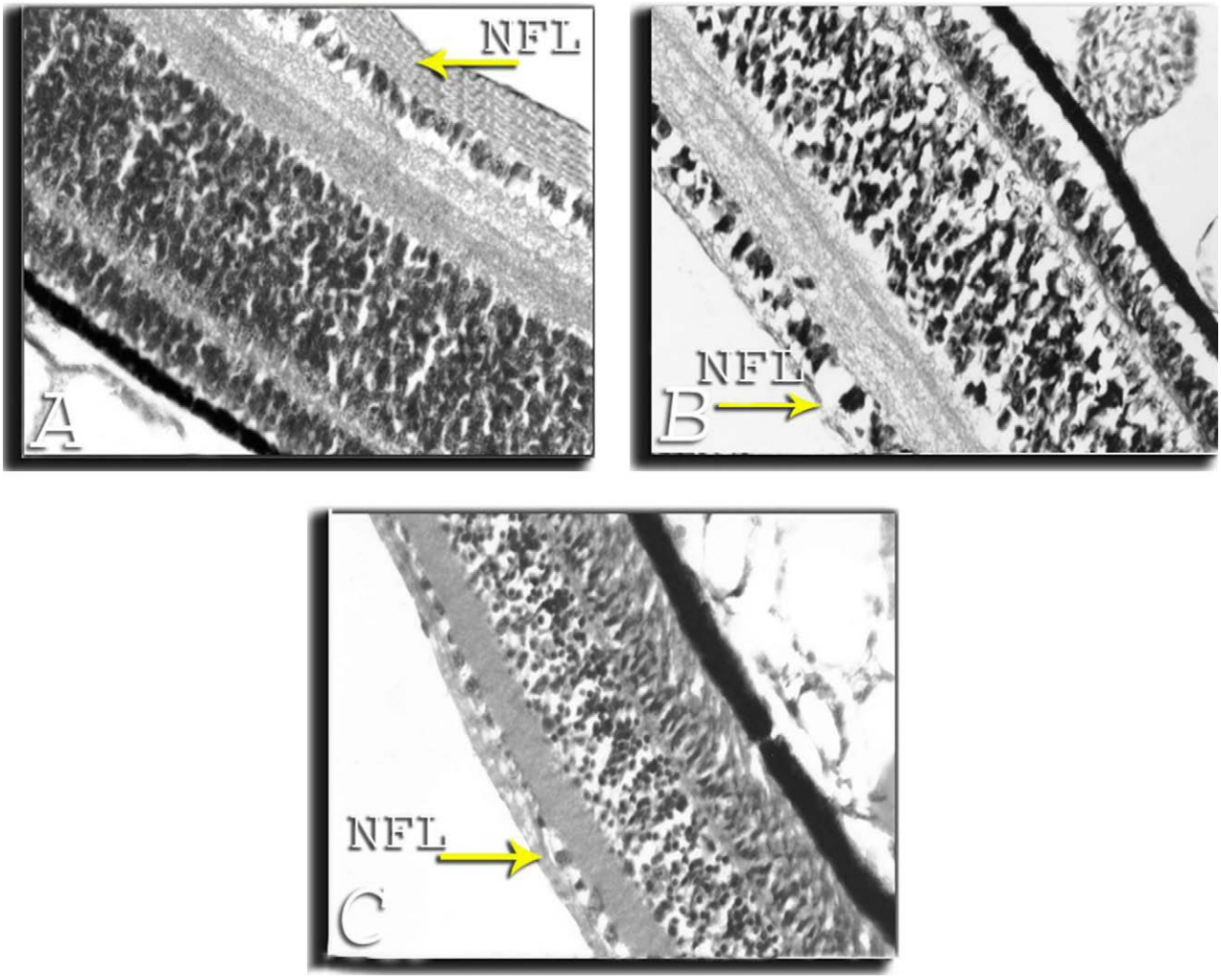

Figure 20 (A) horizontal section of the retina of 16-days old control chick embryo, showing the fibers of the nerve fibers layer (NFL) ⇗ (Holme's stain x 400). (B) A horizontal section of the retina of 16-days old treated (T0) chick embryo ,showing the fibers of the nerve fibers layer (NFL), note its less thick than the control one ⇗ (Holme's stain x 400). (C) A horizontal section of the retina of 16-days old treated (T1) chick embryo, showing the fibers of the nerve fibers layer (NFL), note its less thick than the control one ⇗ (Holme's stain × 400).

glion cell layer also affected as the numbers of the layers cell thick is less and sever degeneration had been occurred, while disproportion effected one the nerves fibers layers, as age advanced (we showed the chronic effect of the drug 16-days old).

The decreased in cellular density and changes of the retina in histological structure of the retina equivalent to the period of injection and to the dose was single. The decrease of the thickness of the layers and less density of the cells was related to direct effect of the drug on the cells of this organ at this time. Also the effect of the haloperidol on the DNA formation and which lead to decreased of the cellular mitotic activates, therefore the retina appeared decrease in thickness and less cell density. These effects was in agreement with many authors whom report the same retardation in growth by using the antidepressant drug as the haloperidol: Lewis et al. (1977); found that the rat of cell acquisition was markedly reduced, and cell cycle time and duration of DNA synthesis phase were clearly prolonged after reserpine drug administration. The haloperidol induced the delayed of the cell cycle and length of DNA synthesis (Patel and Lewis, 1982).

Backhouse et al. (1982), Barochovsky and Patel (1982), and Williams et al. (1992) reported the reduction of DNA synthesis rate was detectable by 4 h after subcutaneous injection of a single dose of haloperidol was less than 50% of that of controls in the forebrain. Holson et al. (1994) added that the exposure to haloperidol reduced the embryonic DNA and protein content and delayed the development of the embryonic cells of the albino rat. Farhoud (1998) found that the administration of haloperidol to the pregnant albino rat resulted in delayed development of seminiferous tubules, which became smaller in size and contained fewer seminiferous cells. Awad (2004) reported that the administration of haloperidol delayed the development of the pancreas of chick embryos. Tolba (2005) said that the haloperidol induced delayed in the formation of the tissue of the testes.

The injection of haloperidol with a dose (equivalent to human therapeutic dose) affected; the retina in (T0, T1 groups) as the tissues had been obviously degenerated with many pyknotic, karyoltic nuclei had been seen. The appearance of cavities, less mitotic figures in basal layer of (neuroplastic cells) and

decreased of the thickness of nerve fiber layers, these changes in histological structure depend on the period of injection.

The finding of the present study were in agreement with the finding of many authors who studies the effected of the antidepressant drug specially the haloperidol on many organs; as Hassan (1990); concluded that the antidepressant induced defect of the development and differentiation of the tissue, so induce apoptosis and necrosis of the retinal cell. Mukherjee and Ghosh (1997) studied that the treatment of haloperidol revealed atrophic degeneration of seminiferous epithelium.

Farhoud (1998), said that the (HL) induced many degeneration in the rat testis, such as, the cells had small nuclei and most of them showed ill-defined nuclei and spermatogonia lost their characteristic feature of rounded nuclei and had vacuolated cytoplasm. Qing et al. (2003) mentioned that the exposure of (PC12) cells to 50micro of metabolite of haloperidol for 24 h resulted in 35–45% loss of cells, certain staining methods revealed this apoptotic nuclear changes and cell death in culture. Awad (2004) found that the haloperidol induced variable degenerative changes in the liver cells; as the cells were irregularly arranged with ill-defined nucleoli, and most of this cells had variable sized vacuolated cytoplasm. and dilated intralobular and intercalated ducts could be seen.

Khalifa (2006); reported that the haloperidol induced many degeneration such as vacuolar degeneration; congestion and haemorrhage; fatty infiltration; fibrosis; cellular necrosis; and pyknosis and karyolysis of cell nuclei. The haloperidol induced neurotoxicity, by reaction with the NMDA receptors on the cells membranes (Zhuravliova et al., 2006). Kim et al. (2008) said that the haloperidol was apparently neurotoxic. The actions of signaling systems associated with GSK-3beta may be key targets for haloperidol, but their effects are distinct. Hisaoka et al. (2008) postulated that the tricyclic antidepressants acutely increased phosphorylation of (cAMP responsive element (CREB)) and increase CREB activity in protein tyrosine kinase (PTK) and extracellular signal-regulated kinase (ERK-) dependent manners, which might contribute to gene expression including (derived neurotrophic factor (GDNF)) in glial cells.

5. Conclusion

From the results of the present work it might concluded that the haloperidol drug has a dangerous effects on the retina and had an inhibitory effect (powerful toxicity) on the cells development. This effect depend on time of the injecting, where at appearance that the drug effected on the tissue from numerous sides:

- Effect on dopamine receptors and reaction with them; whereat its action mechanics reposed on reaction with them.
- Effect on DNA and cellular mitotic; because its principal accountable on cell activity (action of the cell), and on mitotic rate, proliferation and renewal of the cell.
- Effect on cell membranes through dissolution them; because this drug differential by highly acceptability to deliquescence (dissolution) in lipids.
- Effect on cellular enzymes activity of the cells and then making the cellular confused, and making the toxicity for the cells then executed cell death). So that the haloperidol must not be given to the pregnant women in all time of pregnancy specially; before or during the first trimester of pregnancy or.

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