The Possible Neuroprotective Effect of Memantine on Cerebral Cortex after Induction of Transient Cerebral Ischemia in Adult Albino Rats

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ABSTRACT

Background: Transient ischemic attack is the sudden occlusion of one or more brain vessels resulting in an insufficient perfusion of the associated brain area. Therefore, the primary goal of any therapeutic intervention is to minimize neurological impairment. Memantine is a useful drug in many neurological disorders, including Alzheimer's disease.

Aim of the work: This work was aimed to study the possible neuroprotective effect of memantine on the cerebral cortex after induction of acute cerebral ischemia using histological, immunohistochemical and morphometric examination.

Materials and methods: In this study, sixty adult albino rats were used. They were divided into control and experimental groups. The experimental group was divided into four equal subgroups. Each rat in subgroup IIA was given memantine. Subgroup IIB was sham-operated subgroup. Each rat in subgroup IIC was subjected to surgical procedure with induction of transient cerebral ischemia. Each rat in subgroup IID was given memantine after induction of transient cerebral ischemia. Specimens from the left frontal lobe of cerebral cortex were prepared for histological and immunohistochemical study for caspase 3. Morphometric study for measurement of the mean optical density of caspase 3, mean mitochondrial intensity and circularity index of the myelinated axons were evaluated.

Results: After induction of transient cerebral ischemia, Hx. & E.-stained sections from the left frontal lobe of cerebral cortex of an adult albino rat showed loss of organization of the cerebral cortex layers. Vascular changes in the form of thickened endothelial lining and wide perivascular space were noticed. Pyramidal cells became shrunken with loss of their processes. Transmission electron microscopic study revealed a pyramidal cell with indented nucleus and condensed chromatin in the inner nuclear membrane. Myelinated axons showed fissuring of the myelin lamellae and degenerated mitochondria were seen. After administration of memantine, subgroup IID showed improvement of the structural alterations of the cerebral cortex. Apparent normal blood vessels with narrow perivascular space and pyramidal cells with long apical dendrites were seen. A pyramidal cell revealed indented euchromatic nucleus in ultrastructure study. Myelinated axons showed regular arrangement of the myelin lamellae and another with fissuring of the myelin lamellae. Significant increase of optical density for caspase 3 after induction of acute cerebral ischemia while after administration of memantine, no significant changes was seen. The current study revealed highly significant changes in mitochondrial intensity and circularity index of the myelinated axons in subgroup IIC. Significant decrease in mitochondrial intensity in
subgroup IID and no significant changes in circularity index of the myelinated axons were noticed.

**Conclusion:** It can be concluded that memantine, as a neuroprotectant, could be effective in recovery or prevention of structural alterations resulted from transient cerebral ischemia.
Histological and Immunohistochemical Study on the Effect of L-Carnitine on Skeletal Muscles after Experimental Induction of Hyperthyroidism in Adult Albino Rats

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ABSTRACT

Background: Skeletal muscles are important target tissue for thyroid hormones as they are considered major contributors to the basal metabolic rate. Thyroid hormones control basal metabolic rate by modulating energy processes in skeletal muscle. Also they can change muscle protein synthesis that has a major impact on muscle function.

Aim of the work: The aim of this work was to study the structural changes occurring in the gastrocnemius muscle of adult albino rats after experimental induction of hyperthyroidism and the effect of L-carnitine on these changes using histological and immunohistochemical examination.

Materials and methods: Forty adult albino rats were used and divided into control and experimental groups. The latter group was subdivided into two equal subgroups. Each rat in subgroup IIA received 100 mg/kg/day L-carnitine for eight weeks. Each rat in subgroup IIB (hyperthyroidism group) received 40 μg/kg/day L-thyroxine for eight weeks. Each rat in subgroup IIC received the same previous dose of L-thyroxine with 100 mg/kg/day L-carnitine for eight weeks. Hormonal assay for serum T3 and T4 was done. Specimens from the gastrocnemius muscle were prepared for histological and immunohistochemical study. Morphometric study for evaluation of surface area percentage of collagen fibers and optical density of immunohistochemical stain for endothelial nitric oxide synthase (eNOS) were examined.

Results: After induction of hyperthyroidism, Hx. & E.- stained longitudinal sections of gastrocnemius muscle showed degenerative changes in the form of loss of transverse striations, splitting in some fibers and atrophied in others, central and horizontal located nuclei and dilated congested blood vessel. Mallory's trichrome stain showed highly significant increase in collagen fibers distribution. Significant increase in immunohistochemical stain for eNOS was observed. Transmission electron microscopic study revealed disturbance of architecture of sarcomeric pattern and enlarged mitochondria. Indented nucleus with condensed chromatin was seen. After administration of L-carnitine and L-thyroxine (subgroup IIB) Hx. & E.- stained longitudinal sections of the gastrocnemious muscle revealed regressive changes. Regularly arranged muscle fibers with elongated peripheral nuclei with transverse striations and other areas with loss of transverse striations were seen. Mallory's trichrome stain showed no significant changes in collagen fibers distribution. In eNOS immunohistochemical stain showed no significant changes. Regenerative changes were noticed in transmission electron microscopic...
study. Normal sarcomeric pattern was seen but disorganized myofibrils were still present. Elongated peripheral nucleus with dispersed chromatin was also observed. **Conclusion:** Hyperthyroidism-induced myopathy is a common problem which must be focused and researched. Hyperthyroidism-induced myopathy may be prevented or minimized by the use of L-carnitine which has a great role in protection.
Effect of Pancreatic Lipase Inhibitor on the Exocrine Part of the Pancreas in Adult Male Albino Rats: Histological and Morphometric Study

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Abstract

Background: Obesity is an important problem. Orlistat is a pharmacological agent promoting weight loss via inhibiting gastric and pancreatic lipase enzymes.

Aim: This work aimed to study the structural alterations on the exocrine part of the pancreas after short and long periods of administration of pancreatic lipase, orlistat.

Materials and methods: Fifty adult male albino rats were used and divided into control and experimental groups. The latter was divided into three equal subgroups. All rats in the experimental groups were given 12 mg/kg/day orlistat for three days, three weeks and six weeks respectively. The exocrine parts of the pancreas of all rats were examined using histological and morphometric study.

Results: After administration of orlistat for three days, Hx. & E.-stained sections showed apparent normal pancreatic acini formed of pyramidal cells with rounded basal nuclei. Verhoeff’s Van Gieson's-stained sections showed intact wall of dilated blood vessels. Transmission electron microscope showed an acinar cell containing a basal euchromatic nucleus but with indentation. After administration of orlistat for three weeks, multiple vacuolated cytoplasm, dilated blood vessel and focal interruption of the elastic fibers of the wall of dilated blood vessels were detected. Ultrathin sections revealed a central binucleated acinar cell with indentation. After administration of orlistat for six weeks, marked progressive changes in the form of widely separated pancreatic acini, marked dilated congested blood vessels and marked interruption of the elastic fibers in the wall of dilated blood vessels were detected. Ultrathin sections showed shrunken and indented nuclei. Some granules showed peripheral dissolution. In addition, highly significant decrease in the surface area of mean total acinar area and highly significant increase in mean total blood vessels area were detected.

Conclusion: Orlistat could induce unexpected side effects on the exocrine part of the pancreas which were obvious with long period of treatment.
Role of Biological Anti-Tumour Necrosis Factor (Anti-TNF) Agent on Induced Ulcerative Colitis in Adult Albino Rats: Histological and Immunohistochemical Study

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ABSTRACT

Background: Ulcerative colitis (UC) is characterized by significant inflammation of the gastrointestinal tract. The majority of cases with UC are limited to the distal or left side of the colon. UC may be due to genetic susceptibility, environmental factors and an altered host's immune response. Anti-tumour necrosis factor-α therapy as adalimumab is a new trend used in management of UC.

Aim of the work: This work was done to study the effects of biological anti-TNF agent, adalimumab, on the distal colon after induction of ulcerative colitis in adult albino rats using light, scanning and transmission electron microscopes and immunohistochemical examinations.

Materials and methods: Forty adult albino rats were used and divided into control and experimental groups. The latter group was equally subdivided into three subgroups. The rats of the subgroup IIa were injected intraperitoneally with 50 mg/kg adalimumab every other week, for four weeks. The rats of the subgroup IIb were fasted for twenty-four hours before the colonic infusion of acetic acid, 0.3 ml (30 mg/kg) for seven days. The rats of the subgroup IIc were injected intraperitoneally with 50 mg/kg adalimumab every other week, for four weeks, seven days after administration of acetic acid infusion. All the animals were sacrificed after five weeks and subjected to histological and immunohistochemical studies.

Results: After infusion of acetic acid in the colon, Hx. & E.- stained section of the subgroup IIb revealed degenerative changes of the lining epithelium of the colon with distortion of the shape of the crypts of Lieberkühn. Mononuclear cellular infiltration was observed. Scanning electron microscope revealed deep ulcer reaching down to the base of the crypt with disorganized cells at the ulcer margin and wide openings of the crypts. Transmission electron microscope showed widening in the intercellular space. Columnar epithelium with indented nucleus was noticed while the other cell had condensed nuclear chromatin. After administration of adalimumab, subgroup IIc showed regressive changes in the form of straight tubular crypts lined with simple columnar epithelium and goblet cells. Scanning electron microscope showed areas with regular shaped openings of the crypts but others still revealed wide openings. Regressive changes were seen by transmission electron microscope in the form of well-defined intercellular junction between the adjacent columnar cells in some areas but still wide in other areas. Columnar cells with normal nuclear chromatin distribution were seen. Immunostaining for TNF-alpha in subgroup IIb showed positive cytoplasmic immune reaction in the absorptive cells of crypts. Meanwhile, subgroup IIc revealed weak positive cytoplasmic immune reaction in both absorptive cells of crypts.

Conclusion: From this study, it could be concluded that adalimumab represented one of the biological drugs that considered the drugs of the future. It helped in the improvement of ulcerative colitis and showed to have better long term outcome.
Effect of aromatase inhibitors on the endometrium and ovary with their possible role in ovulation in adult albino rats: A histological, immunohistochemical, morphometric, and hormonal assay

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ABSTRACT

Background: Aromatase inhibitors act by inhibiting estrogen synthesis and depletion of its concentrations in the circulation.

Aim: The aim of the study was to investigate the effect of exemestane and letrozole on the endometrium and ovary with their possible role in ovulation in adult albino rats.

Materials and methods: Thirty adult female albino rats were used and divided into control and experimental groups. Rats in the experimental group were further divided into subgroup IIA and subgroup IIB. In subgroup IIA each rat was given exemestane at 1 mg/kg/day and in subgroup IIB each rat was given letrozole at 5 mg/kg/day by means of a gastric tube for five consecutive ovarian cycles. Specimens from their ovaries and endometrium were taken and prepared for H&E staining and for immunohistochemical staining for vascular endothelial growth factor study. Morphometric study of endometrial thickness and surface area percentage of immunoreaction in the endometrium was evaluated. Hormonal assay of luteinizing hormone and follicular stimulating hormone was carried out.

Results: Significant decrease in endometrial thickness was observed in the exemestane treated group. The letrozole-treated group revealed significantly thickened endometrium. The exemestane-treated group showed markedly disturbed ovarian architecture in the form of thickened germinal epithelial cell layer and multiple corpora lutea with atretic follicles. The letrozole-treated group revealed an ovarian cortex with multiple stages of follicular development. The vascular endothelial growth factor immunoreaction of the letrozole-treated group showed significant highly positive cytoplasmic reaction. Significant decrease in luteinizing hormone level in the exemestane group and significant increase in the letrozole group were detected.

Conclusion: It is concluded that letrozole improved the endometrial thickness and may have a role in ovulation induction. In contrast, exemestane led to disruption of the endometrium and ovary. Therefore, not all aromatase inhibitors help in ovulation.
Role of Dexamethasone alone and in Combination with Quercetin on Urinary Bladder after Administration of Ifosfamide: A Histological, Immunohistochemical and Morphometric Study

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Abstract

Background: Ifosfamide is a broad spectrum antineoplastic agent. Dexamethasone inhibits the activity of a variety of cytokines. Quercetin is a flavonoid with an antioxidant effect.

Aim: this work is aimed to study the possible protective role of dexamethasone alone and in combination with quercetin on ifosfamide-treated urinary bladder.

Materials and methods: Sixty adult albino rats were used and divided into six groups. Groups I, II and III are control, dexamethasone-treated and dexamethasone and quercetin-treated group respectively. Group (IV) ifosfamide-treated group: Each rat was injected with ifosfamide. Group (V) ifosfamide and dexamethasone-treated group: Each rat was injected with ifosfamide and three doses of dexamethasone. Group (VI) Ifosfamide, dexamethasone and quercetin-treated group: Each rat was injected with ifosfamide and three doses of dexamethasone and quercetin. Urinary bladder specimens were processed for histological and immunohistochemical staining for iNOS and NF-kappaB followed by different morphometric examinations.

Results: Group (IV) revealed epithelial ulceration and vacuolated cells. Group (V) showed partially restored thickness of the urothelium with vacuolated cells. Group (VI) showed restored epithelial integrity with reduced cytoplasmic vacuoles. Electron microscopic examination of the urothelium showed indented nuclei and dilated intercellular spaces in group (IV). After administration of dexamethasone, indented nuclei and partially dilated intercellular space were seen. In group (IV), urothelium revealed apparently normal nuclei with almost intact tight junctions. Highly significant increase in mast cell count in group IV but non-significant increase after administration of both dexamethasone and quercetin were noticed. Optical density of immuno-reaction for iNOS and NF-kappaB showed highly significant increase in group IV. Significant increase was detected in group V for NF-kappaB but non-significant increase in group VI for both immunohistochemical stains was observed.

Conclusion: It could be concluded that both dexamethasone and quercetin showed better protective role against the toxic effects induced by ifosfamide rather than using dexamethasone alone.
Effect of Stem Cells Transplantation on Amiodarone-Induced Hepatic Changes in Adult Male Albino Rats: Histological and Immunohistochemical Study

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Abstract

Background: Bone marrow derived mesenchymal stem cells (BM-MSCs) can be differentiated into various cells including hepatocytes which have the ability to open a new strategy to treat many diseases.

Aim of the work: This study was designed to evaluate the possible effect of stem cells transplantation on amiodarone-induced hepatic changes in adult male albino rats through intravenous and intrahepatic injection.

Materials and methods: Seventy male adult albino rats were used. Ten rats were used as a source of BM-MSCs and sixty rats were divided into two groups; control and experimental. Control group included twenty rats. Experimental group (II) included forty rats and subdivided into four equal subgroups; subgroup IIa (amiodarone, cordarone, administration for six weeks), subgroup IIb (after four weeks of amiodarone withdrawal), subgroup IIc (intra-venous BM-MSCs treated) and subgroup IIId (intra-hepatic BM-MSCs treated). Liver specimens were processed for H &E, Mallory’s trichrome and immunohistochemical stains for Alpha fetoprotein (AFP) and Endoglin CD105 Antibody (CD105). Morphometric study was used to determine the surface area for collagen fibers and the optical density of AFP.

Results: Subgroup IIa showed disturbed arrangement of hepatic cords, dilated congested central vein and nuclear changes. Subgroup IIb revealed more destructive changes after stopping of the drug. Highly significant increase of surface area for collagen fibers in both subgroups was observed. In subgroup IIc, there were partial improvement of the histological findings while in subgroup IIId, there were marked improvement. No significant increase of surface area for collagen fibers in both subgroups. The optical density of AFP positive cells showed highly significant increase in BM-MSCs treated subgroups. BM-MSCs treated subgroups showed positive reaction to CD 105 immunostaining.

Conclusion: BM-MSCs can improve the changes associated with amiodarone-induced liver injury in adult male albino rats. The structural alterations improved in the intra-hepatic injection more than the intravenous one.
Effect of Leflunomide on the Lung of Adult Albino Rats and Role of Pentoxifylline Co-administration: A Histological and Morphometric Study

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Abstract

Background: Leflunomide is an immunosuppressive compound that is effective in the treatment of autoimmune disease and rheumatoid arthritis. It has anti-inflammatory and antiproliferative properties. Pentoxifylline is used to treat vascular and cerebrovascular disorders.

Aim of the work: This work is aimed to study the structural changes in the lung of adult albino rats after administration of leflunomide alone and in combination with pentoxifylline using histological and morphometric study.

Material and methods: In this study forty adult albino rats were used. They were divided into two groups, control and experimental. The latter group was subdivided into three equal subgroups. Each rat in subgroup IIA received 12mg/kg/day pentoxifylline. In subgroup IIB, each rat received 2 mg/kg/day leflunomide. In subgroup IIC, each rat received co-administration of 12mg/kg/day pentoxifylline and 2 mg/kg/day leflunomide. All animals were sacrificed at the end of the experiment, after eight weeks. Specimens from the lung was taken and prepared for light and transmission electron microscopes and morphometric study for thickness of the inter-alveolar septa.

Results: H&E stained sections of group II revealed a marked alternation in lung histological structure as; many alveoli appeared collapsed with thickened inter-alveolar septa. Cellular infiltration of bronchiolar, perivascular and the inter-alveolar septa with mononuclear cells and extravasated RBCs in the alveolar lumen could be detected. On the other hand, examination lung section of group III revealed that most of the changes which were observed in the previous group decreased but did not disappear completely.

Electron microscopic results of group II revealed degeneration of pneumocytes type II as; extensive vacuolation of the cytoplasm and dilatation of RER. Vacuolated swollen mitochondria with damaging of their cristae were also detected. The lamellar bodies appeared to be deprived from their secretory surfactant material with many nuclear changes. There was interstitium inflammatory cells infiltration.

While in group III, most of the observed changes in leflunomide treated group were decreased. Pneumocytes Type II appeared nearly similar to the control.

Morphometric results:
There was a highly significant increase in the mean thickness of the inter-alveolar septa in leflunomide treated rats compared to control rats. Meanwhile, a non significant increase was noticed in group III.