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Comparative studies on the effect of Prozac drug and Barely grains on the skeletal muscles of mice: behavioral and histological studies

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ABSTRACT

The purpose of this study was comparing between the biotoxic action of Prozac and Barley grains on skeletal muscle of depressed mice model. Forty adult male mice (*Mus musculus*) (25 ± 5 g.) assigned into four groups: -ve control with normal social environment, +ve control (socially isolated), Prozac-group (socially isolated) injected with (0.06 mg Prozac / mouse / day) and Barely-group (socially isolation) supplemented with Barley grains instead the usual food (5g. Barley/mouse/day) for 30 days. Forced swimming and tail suspension tests are used to assay mice mood levels. Biopsies of gastrocnemius muscle were fixed in Aoyama's fluid and 10% buffered formalin solution for light microscopy processing stained with Hematoxylin and Eosin, Masson's Trichrome. Barley-group did not show any abnormal behavior but Prozac-group became less active and their responsiveness to external stimuli was decreased. Barely-group reduced immobility in compare to Prozac group. Prozac-group showed increase in body weight but the Barely-group showed decrease. It was assessed tissue protected situation in the presence of Barely supplementation. In the other hand, Prozac-group showed myofibers with variation in size, sarcolemma giving step-like offsets, increased collagen deposition, some regions of affected muscle fibers devoid of Golgi bodies. Our results showed that Barely reduce risk factors.

Keywords: Prozac drug, Barley grains, Behavior, Histology, Mice.

INTRODUCTION

Some types of depression tend to run in families, suggesting a genetic link. However, depression can occur in people without family histories of depression as well (Tsuang and Faraone, 1990). Genetics research indicates that risk for depression results from the influence of multiple genes acting together with environmental or other factors (Tsuang *et al.*, 2007). Depression co-exists with other serious medical illnesses such as heart disease, stroke, cancer, aids, diabetes and Parkinson's disease. Studies have shown that people who have depression in addition to another serious medical illness tend to have more severe symptoms of both depression and the medical illness (Cassano and Fava, 2002). Serotonin uptake inhibitors are the drugs of choice for treating depression because of their efficacy, tolerability and superior safety in overdose (Pollock, 2001).

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Prozac (PR) is an antidepressant of the selective serotonin reuptake inhibitor class. PR is approved for the treatment of major depression, obsessive-compulsive disorder, bulimia nervosa, panic disorder and premenstrual dysphoric disorder (Pollock, 2001). Among the common adverse effects associated with PR are nausea, insomnia, somnolence, anorexia, anxiety, nervousness, asthenia, tremor (Settle and Settle 1984) and Akathisia (Leo, 1996). Also, sexual side effects affect patient's quality of life and, in long-term treatment, can lead to non-compliance and relapse (Lee *et al.*, 2010). It was found that PR decreased right ventricular hypertrophy and reduces pulmonary vessels thickness in rats. These results suggested that chronic PR treatment can lead to a decrease in the manifestation of pulmonary hypertension symptoms (Kozhevnikova and Medvedeva, 2007). The inhibition of cardiac Ca^{2+} , Na^{+} and K^{+} and vascular Ca^{2+} channels by PR may explain most cardiovascular side effects observed occasionally with the drugs during the chronic treatment. This inhibitory effects may result in antiarrhythmic /proarrhythmic actions (Park *et al.*, 2007). Also, the locomotor activity were affected by neonatal PR treatment as PR administration has long-lasting effects on the function and structure in the somatosensory system (Lee, 2009).

Consumption of diets high in whole grains has been recommended in the 2005 Dietary Guidelines and are reported to have a number of beneficial health effects including reduced risk of cancer (Jacobs *et al.*, 1998) and cardiovascular disease (Truswell, 2002). Hinata *et al.* (2007) suggested that a well-regulated lifestyle and long-term intake of high dietary fiber may have beneficial effects on metabolic process.

Barley (B) is a cereal grain derived from the annual grass *Hordeum vulgare*. It serves as a component of various health foods. It is used in soups and stews, and the grain is used locally in bread, biscuits, and the traditional peremeal bannock (Martin *et al.*, 2008). B has been referred in Arabian traditional medicine for the treatment of different central nervous system (CNS) diseases, mainly depression. Narrated 'Aisha: (the wife of the Prophet) I heard Allah's Apostle saying, 'The Talbina soothes the heart of the patient and relieves him from some of his sadness. (Volume 7, Book 65, Number 328. Nevertheless). In this work, comparative studies on the effect of antidepressant drug (Prozac) and Barley grains with antidepressant-like effect on skeletal muscles of male mature mice were made through behavioral and histological alterations.

MATERIAL AND METHODS

Animal selections and care

Healthy 40 adult male Swiss albino mice (*Mus musculus*) weighting (25 ± 5 g.) with their mean age (60 ± 7 days) from the Animal House of Medical Research Institute (King Abdul Aziz University) were used in the present study. Animal models of psychiatric disorders, including socially isolated male mice for 7 days before the experiment (Pinna *et al.*, 2008) were used. The mice were assigned into four main groups, each group 10 mice classified as: -ve control (normal social environment), +ve

control (socially isolated), Prozac-group (socially isolated) received an intraperitoneal injection ($2 \text{ mg PR} / \text{kg} / \text{day}^{-1}$) and Barely -group (socially isolated) received Barley grains instead the usual food ($200 \text{ g. B} / \text{kg} / \text{day}^{-1}$). All animal experiments were done in accordance with animal protection guidelines approved by the Research and Ethical Committee of Medical Research Institute.

The used chemical

Prozac has an empirical formula of " $\text{C}_{17}\text{H}_{18}\text{F}_3\text{NO}$ " and molecular weight of 309.3 in the form of tablets (20 mg each) by EI-Nil pharmaceutical, chemical industries CO. Cairo, A.R.E., it is available under the international trade name Prozac.

Selection of doses

One dose is equivalent to the low human therapeutic dose for prophylactic treatment (20 mg/day) was chosen (Schou and Baastrup, 1967). Paget and Barnes formula (1964) was applied to Swiss albino mice, as it considers the species differences to determine the equivalent doses of Prozac given to Swiss albino mice. After 30-days, the animals were left overnight (food and water permitted) and the following parameters were comprised in the present investigation.

I. Animal behavior

1. Mice belonging to the four groups observed daily for any behavioral changes and number of dead mice were recorded. At the beginning of the experiment and weekly, body weights were detected.
2. The behavioral despair tests (the animal has resigned escaping):
 - A- Porsolt test or forced swimming test (FST) (Guadarrama *et al.*, 2008) is used to measure the effect of antidepressant drugs on the behavior of mice.
 - B- The tail suspension test (TST) (Perona *et al.*, 2008) is used to assay mood levels in rodents.

II. Histological examination

Animals sacrificed between 9 and 11 am, the left mice gastronomic muscles (Arshaduddin, 2004) were excised, quickly cut into small pieces (about 5mm) to allow good fixative penetration.

- 1- For the general histological evaluation, sections (5µm thick) fixed in 10% neutral formalin and stained with Hematoxylin and eosin (H&E) (Bancroft, 2007). The diameter of muscle fibers in the longitudinal section were measured and examined using object-oriented lens 10X, and the average values are calculated for every ten readings of each sample.
- 2- For demonstration of collagen fibers, sections (5µm thick) fixed in 10% neutral formalin and stained with Masson's Triple Stain (Calling *et al.*, 1985).
- 3- For demonstration of Golgi bodies, Aoyama silver nitrate impregnation technique was applied (Gotenboy and Beans, 1950).

III. Statistical analysis

The results are presented as mean \pm standard error. One-way ANOVA followed by Dunnett's multiple comparison tests were used (Arshaduddin, 2004).

RESULTS AND DISCUSSION

In this study a comparative observations were performed between the Barely -treated group and the Prozac-treated group with refer to the -ve control -group and +ve control group as regard to behavioral, mortality, body weight and histopathological changes .

I. Animal behavior

- ve control -group and Barley- group did not show any specific abnormal behavior. However, mice treated with Prozac drug showed changes in the general behavior, they became less active and their responsiveness to external stimuli was decreased , but mice from +ve control-group showed more changes in the general behavior than other groups , some of them stopped food eating from the second week, mice were fear responsive and very aggressive than others as recorded before (Pinna *et al.*,2008).

Table (1) showed that the mice mortality induced by administration of Prozac drug increased than - ve control and Barely -group , although in the present study the low therapeutic dose was used.

Since a relationship between depression and fatigue has been well established,(Alder,2004) , it was determined to evaluate the antidepressive effect of both Barely and Prozac using the tail suspension test (TST) (Steru *et al.*, 1987) that, in parallel with the forced swimming test (FST) (Porsolt *et al.*, 1978) which has been proposed as a primary screening test for antidepressant drugs. At (Table 2) ,it was noticed that Barely reduced immobility and increased swimming without affecting climbing behavior than -ve control group and Prozac -group respectively as shown before in rats treated with the extract of *Tagetes lucida* Cav (10, 50, 100mg/kg /day⁻¹) which possesses antidepressant-like properties (Guadarrama *et al.*, 2008).Also, decreased immobility a correlate of antidepressant activity, has been observed in NET KO mice (Xu *et al.*, 2000) and DAT KO mice (Spielewoy *et al.*, 2000)) and this might indicated that Barely had antidepressed effect where most drugs that are clinically effective antidepressants in humans produce reduced immobility in the rodent forced swim test (Porsolt, 1978).

However, several models of depression, including those produced by withdrawal from amphetamine, withdrawal from ovarian hormone treatments that simulate pregnancy and estrogen deficiencies caused by aromatase knockout increase forced swim test immobility and decrease climbing without affecting swimming (Dalla *et al.*, 2004) and this antagonist the present results. However, there is some debate between scientists whether increased immobility instead demonstrates a learning within the animal and a positive behavioral adaptation, i.e. the animal has learnt it can't escape and is conserving energy until it is removed by the experimenter (Demouliere *et al.*, 2005).

Table. 1: The mortality rate of animals during the experimental period.

Exp.groups	Mice No.	Dead No.	Surviving No.	Mortality %
- ve control	10	0	10	0%
+ ve control	10	3	7	30%
Barley	10	0	10	0%
Prozac	10	2	8	20%

Table. 2:Statistical analysis of FST and TST period .

Exp. Group	Time /sec.	- ve control	+ ve control	Barley	Prozac
F.S.T.	mean	2.133 \pm	1.270 \pm	1.700* \pm	1.837 \pm
	\pm S.E	0.433	0.355	0.635	0.113
T.S.T.	mean	2.900 \pm	1.200 \pm	1.903* \pm	2.767 \pm
	\pm S.E.	0.100	0.551	0.806	0.521

* Significantly different from the control, P < 0.05 .

Animal weight

This study examined the relative likelihood of the occurrence of weight gain with Prozac- administration where Prozac- group gained non significant increase in weight than their matched -ve control-group as the drugs commonly used in the treatment and prophylaxis of depression, mania and psychotic illness have, as one of their prominent side effects, the ability to increase appetite, stimulate carbohydrate craving and promote weight gain (Conley *et al.*,1998) but Barely-group showed a significant decrease (Table 3).

Table. 3: Statistical analysis of body weight/ g. during the experimental period.

Expe. Group	Week	-ve control	+ ve control	Barley	Prozac
First	mean \pm	31.500 \pm	30.467 \pm	30.500 \pm	28.875 \pm
	S.E	1.500	1.245	1.258	0.554
Second	mean \pm	31.900 \pm	31.700 \pm	29.933 \pm	30.750 \pm
	S.E	1.600	0.100	1.572	0.866
Third	mean \pm	32.850 \pm	31.767 \pm	28.533* \pm	31.800 \pm
	S.E	1.650	1.126	1.362	1.045
Fourth	mean \pm	32.850 \pm	31.933 \pm	26.333* \pm	33.425* \pm
	S.E	1.650	1.097	1.202	1.674

* Significantly different from the control, P < 0.05.

Microscopical Observations

1- Hematoxylin and Eosin (H&E)

-ve control- group , showed in cross sections , polygonal or oval shaped myofibers , each myofiber is invested by a delicate connective tissue covering, the endomysium. Myofibers are bundled together into groups, or fascicles ,the "bundles" are joined together by the perimysium. The muscle as a whole is covered with connective tissue, represented the epimysium which contained blood capillaries (Fig.1). In longitudinal section, each muscle fiber is long cylindrical in form with diameter (302.211 \pm 9.898 μ m) (Table 4) .

+ve control -group, showed myofiber with ill defined striation , an abundance of central nuclei and evidence of degeneration (small fibers with inflammatory infiltrate),the inflammatory infiltrate was composed of lymphocytes and suggestive of an ongoing chronic-active inflammatory process (Fig. 2) with significant decrease in the diameter in compare with - ve control (Table 4) .

Barely - group, showed normal arrangement of oval-shaped muscle fibers have peripheral located nuclei grouped into fasciculi enclosed with perimysium . No evidence of myofiber

atrophy or regeneration (Fig.3). In longitudinal section the striated skeletal muscle fiber with uniform in their size in compare with – ve control –group (321.224 ± 23.001 vs. $302.211 \pm 9.898 \mu\text{m}$).

Table. 4: Statistical analysis of histological measurements .

Exp. Group Variables		- ve control	+ ve control	Barley	Prozac
Fiber	mean	$302.21 \pm$	$158.96^* \pm$	$321.22 \pm$	$165.61 \pm$
diameter/ μm	\pm S.E	9.89	7.58	23.01	20.04

Prozac –group: Prozac caused myopathic alterations in gasteronemius muscle (Fig.4) as Citalopram which produced myopathic alterations in soleus muscle resembling those previously induced with other cationic amphiphilic drugs (Rautakorpi *et al.*, 1982). Also, histological examination of muscle sections of mice treated with high dose of Prianil C-R revealed destruction of muscle fibers in some affected areas (Mohamed, 2003). Variation in the size of the muscle fibres was observed, some were small and narrow (atrophied), others were of usual size and some were hypertrophied (Table 4). Atrophied muscle fibers were also observed in flexor digitorum muscle of mice treated with Prianil C-R (Mohamed, 2003).

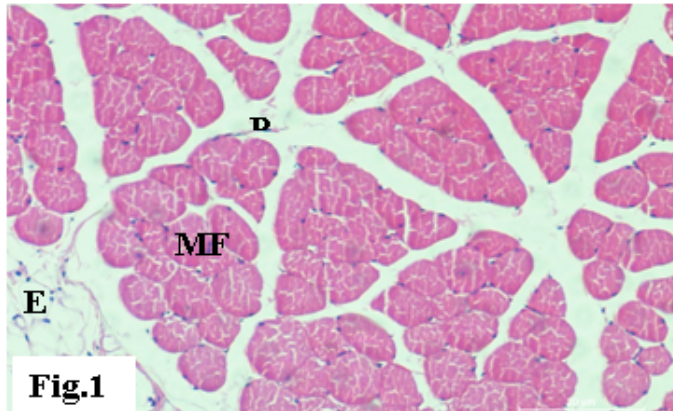


Fig. 1: Light image of transverse section of gastrocnemius muscle of -ve control-group with oval muscle fibers (MF), perimysium (P) and epimysium (E) (H&E, X 10).

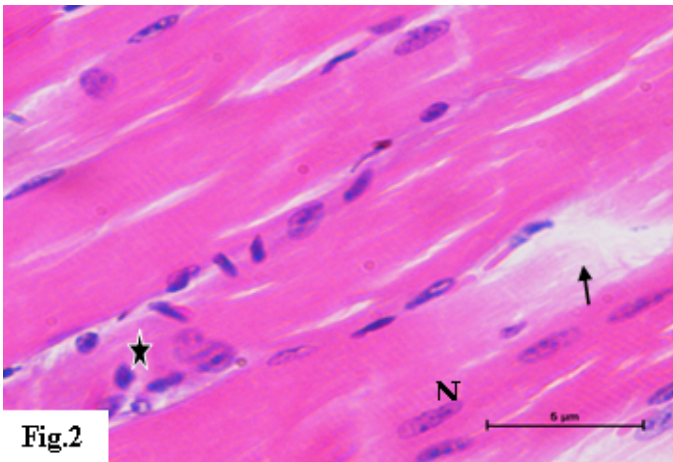


Fig. 2: Light image of longitudinal section of gastrocnemius muscle of +ve control-group with ill defined striation has some centrally placed nuclei (N), necrotic region (arrow) and cellular infiltration (stars) (H&E, X 100).

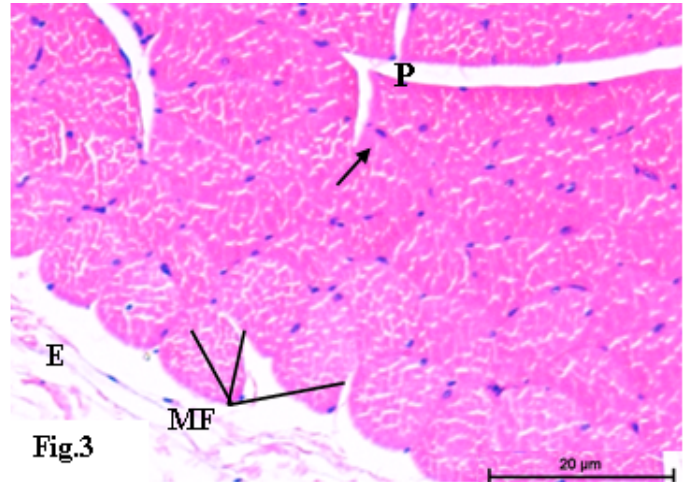


Fig. 3: Light image of transverse section of gastrocnemius muscle of Barely-group showing normal arrangement of oval-shaped muscle fibers (MF) have peripheral located nuclei (arrow) enclosed with perimysium (P). Note, epimysium (E) (H&E, 10x).

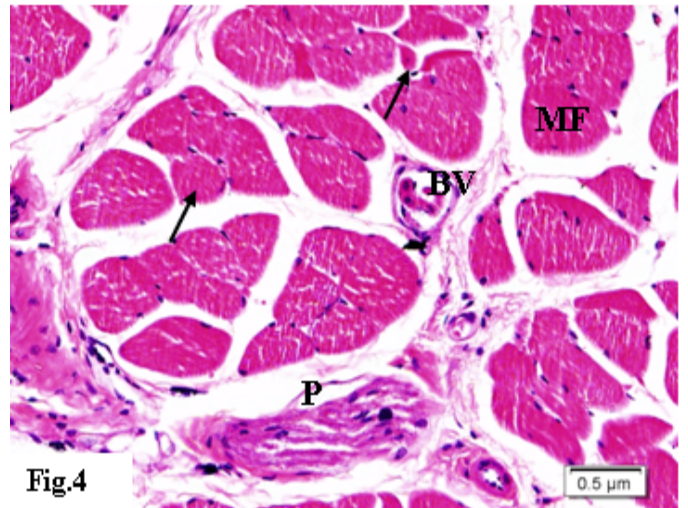


Fig. 4: Light image of transverse section of gastrocnemius muscle of Prozac-group with increased amount of perimysium (P) between eosinophilic muscle fibers (MF), congested blood vessels (BV) and atrophied one (arrow) (H&E, X 40).

2- Aoyama – silver nitrate preparation

-ve control- group, showed obvious argentophilic cross striation in each muscle fiber and the nuclei of muscle fiber were difficult to be seen due to their argentophobic nature. In these preparations, the Golgi bodies appeared as closely packed argentophilic bodies along the muscle fibers in associations with the cross striations (Fig. 5).

+ve control –group showed myofibers with variation in muscle fibers appearance have different diameter and show sites of damage and irregular sarcolemma. Golgi bodies appeared as brown granules associated with cross striation in the form of narrow bands (Fig. 6).

Barely – group, showed nearly normal muscle fibers have well demonstrated striation and few ones with abnormal washed striation and this mean that some muscle fibers showed clear loss of Golgi granules (Fig. 7).

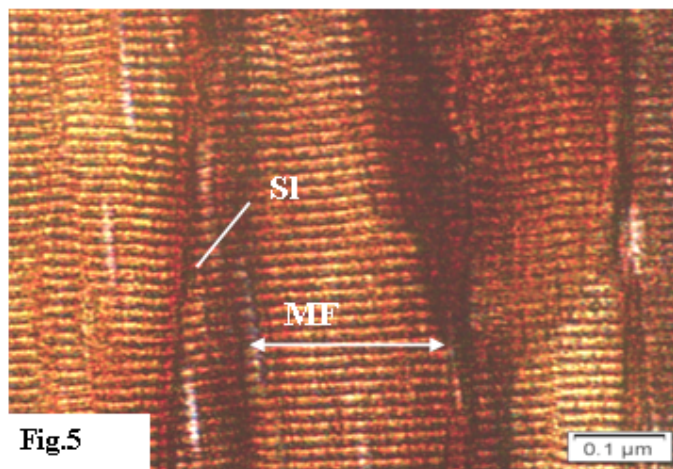


Fig. 5: Light image of longitudinal section of gastronemius muscle of -ve control- with obvious cross striations in all muscle fibers (MF) limited by regular sarcolemma (SI) (AgNo₃, X 100).

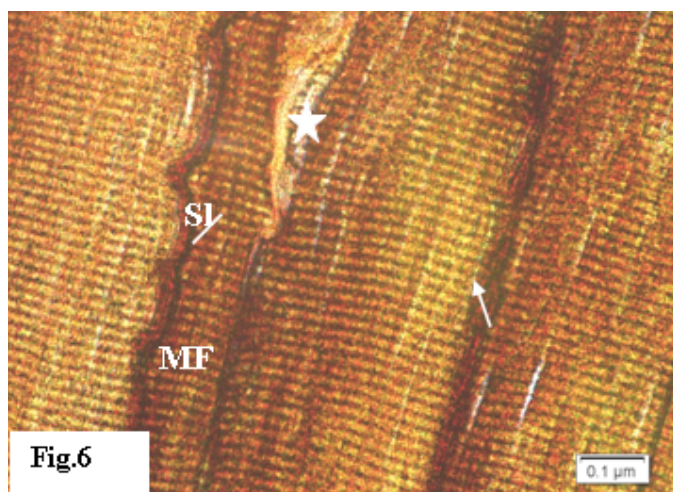


Fig. 6:Light image of longitudinal section of gastronemius muscle of +ve control -group with different diameter muscle fibers (MF), site of damage (star), irregular sarcolemma (SI) and Golgi bodies appeared as brown granules associated with narrow bands of cross striation (arrows) (AgNo₃,X100).

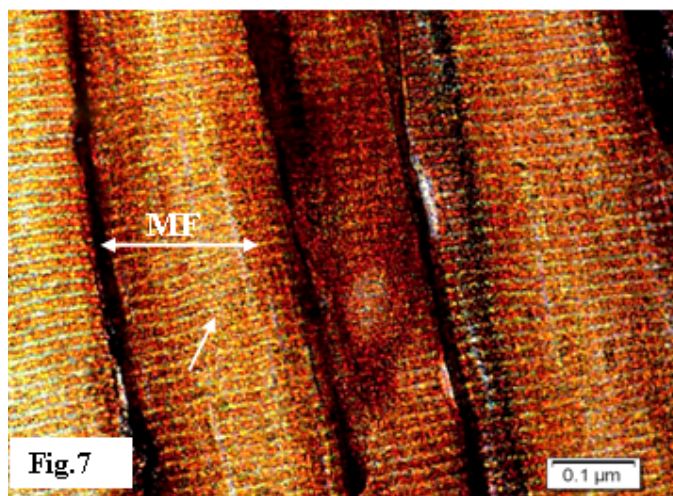


Fig. 7: Light image of longitudinal section of gastronemius muscle of Barely-group where nearly normal muscle fibers (MF) have well demonstrated striations and few ones with washed striation (arrow) (NgNo₃, X 100).

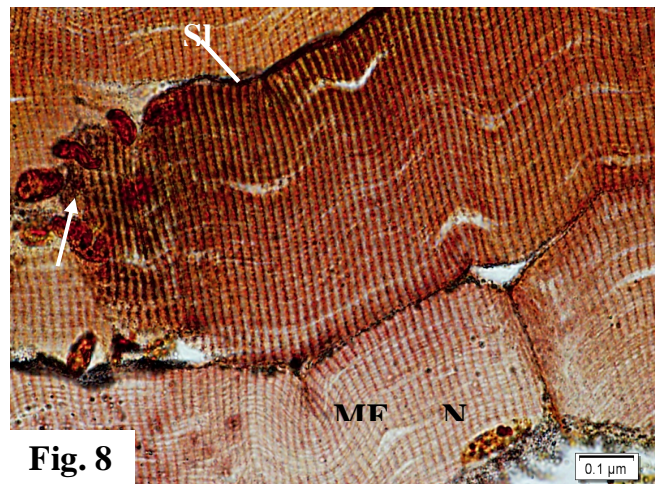


Fig. 8: Light image of longitudinal section of gastronemius muscle of Prozac-group where constrictive deformation of muscle fibers with cellular infiltration (arrows), affected muscle fibers devoid of Golgi bodies (MF), thick sarcolemma (SI) and false argentophilic myonucleus (N) (AgNo₃, X 100).

Prozac -group : Aoyama silver nitrate preparation showed abnormal washed striation of some areas in the muscle fibers of mice treated with Prozac (Fig.8) , similar to the present findings, De Freitas *et al.* (1988) detected a loss of muscle fiber striations in groups of patients skeletal muscle fibers suffering from alcoholic cardiomyopathy. Abnormal washed striation was also observed by Mohamed (2003) in the flexor digitorum muscle of mice treated with with Prianil C-R (antidepressive drug).

3-Masson's trichrome stain

-ve control- group with scanty amount of dense blue collagen fibers determined in both endomysium and perimysium (Fig.9).

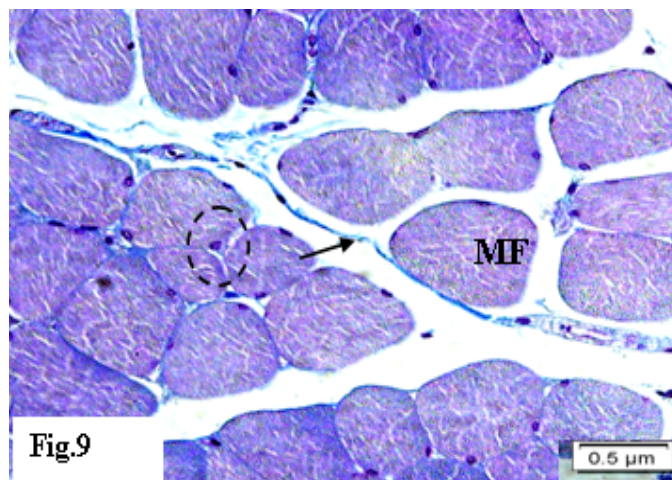


Fig. 9: Light image of transverse section of gastronemius muscle of -ve control group with scanty blue - colored collagen fibers (dashed line) in endomysium between the myofibers (MF) and thin perimysium (arrow) (Masson's trichrome , 20X).

+ve control -group revealed in longitudinal section ill striated mega- fiber markedly attenuated with collagenous sheath and randomly distributed foci of inflammation and in transverse

section also, endomysial and perimysial fibrous tissue increased that might occur during a chronic inflammatory process (Fig.10).

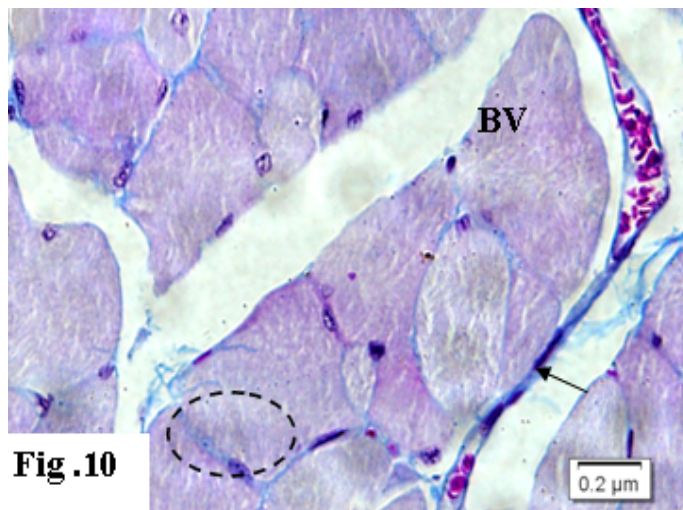


Fig. 10: Light image of transverse section of gastrocnemius muscle of +ve control-group with thick sheath of dense blue-stained collagen fiber including the endomysium(dashed-line) and perimysium (arrow) ,congested blood vessel (BV) (Masson Trichrome , X 10) .

Barely – group revealed thin normal blue-stained perimysium and endomysium which mean that there was a small amount of collagen fibre between the gastrocnemius cell (Fig.11) .

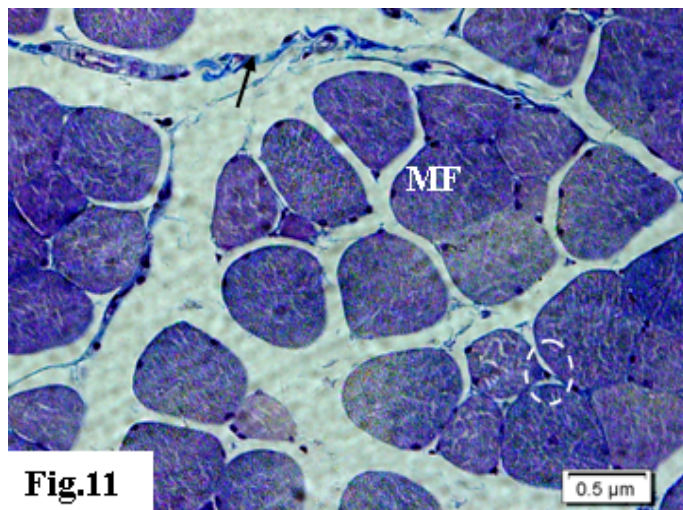


Fig. 11: Light image of transverse section of gastrocnemius muscle of Barely-group with nearly normal blue-stained perimysium (arrow) thin blue- stained endomysium (dashed-line) inbetween muscle fibers (MF) (Masson Trichrome , X 10).

Prozac –group ,revealed increased collagen deposition/my- fibrosis with degenerative foci where myotonic dystrophy like structure characterized with profusion of central nuclei and ring fibers appeared (Fig.12) like centronuclear (myotubular myopathy) which is characterized by small myofibers with central nuclei, and central areas without contractile filaments, like immature fetal muscle (Jungbluth *et al.*, 2008) .

In the current study , stained sections of mice muscle of treated Prozac and +ve control revealed the presence of cellular

inflammatory infiltration in between the damaged muscle fibers as in flexor digitorum muscle of mice treated with Prianiil C-R (Mohamed, 2003) and in soleus muscle of rat treated with Triamcinolone acetate (fluorinated steroid) (Lee *et al.* ,2010).

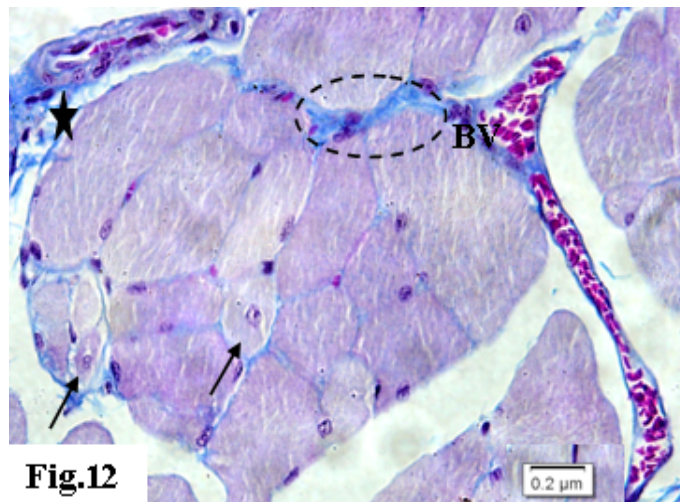


Fig. 12: Light image of transverse section of gastrocnemius muscle of Prozac-group with myotonic dystrophy- like structure characterized with profusion of central nuclei and ring fibers (arrows) , more collagen fibers in both endomysium (dashed-line) and perimysium (star) .Congested blood vessels (BV) (Masson Trichrome , X40) .

CONCLUSION

This is the first research to demonstrate that Barely strongly attenuates injury in skeletal muscles of mice exposed to depression (social isolation)where examination of gastrocnemius muscle sections from the Barely- group by high resolution light microscopy did not reveal any abnormalities as compared with wild type littermates .It was believed that these data are important to develop futures therapies aiming to preserve muscle structure in a psychiatric situation. It is possible that the strategic provision of certain vitamins,amino acids,minerals,trace elements or fatty acids in amounts sufficient to correct biochemical abnormalities,nutritional deficiencies or erroneous eating habits will be therapeutic in preventing or treating many psychiatric and emotional disorders.

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