INDUCTION OF DEPRESSION MODEL IN MICE:

IMPLICATION OF DIFFERENT RESERPINE DOSES

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ABSTRACT

Depression is a mood disorder whose main clinic characteristics include lasting low motion, decrease in motivate ability and slowness in function of thinking and recognizing. It is showed in national survey that the suicide rate of people suffering from depression is 20 times higher than that of normal people. The present study aimed to select the most suitable dose of reserpine for induction of depression in mice with minimal side effects and minimal mortality rate. Depression was induced in mice by a single i.p. reserpine injection at different dose (0.1, 0.5 and 1 mg/kg) at the day 1, then forced swimming test was performed 1 hour later at the first day. The duration of the experiment was 2 days. The mortality rate was recorded, The brain was excised and prepared for determination of the content of the Adenosine monophosphate (AMP), adenosine Diphosphate (ADP) and Adenosine triphosphate (ATP), Monoamine neurotransmitters (5-HT, DA and NE), Malondialdehyde (MDA), Nitric oxide (NO), Glutathione reduced (GSH), oxidized (GSSG) and 8- hydroxyl-2-deoxyguanosine (8-OHDG). The forced swimming test and number of jumping showed no significant difference between different doses while the mortality rate was markedly variable. The results concluded that the most suitable reserpine dose for inducing depression with minimal mortality was 0.1 mg/kg of body weight.
Key words: Depression – reserpine.

INTRODUCTION

Depression is one of the most common neuropsychiatric disorders that affect approximately 20% of the world population (Thakare and Patel, 2015). It can be caused by one or more changes in the brain, which may or may not be directly related. These changes may include monoamine neurotransmitters depletion, cellular atrophy, neuronal death or decreased neurogenesis (Hurley *et al.,* 2014). Also depression is a neuro-psychiatric illness that involves the whole body, mood and thoughts and affects the way a person eats, sleeps, feels about himself or herself and thinks about things. It is a mood disorder that causes a persistent feeling of sadness and loss of interest. Also called major depressive disorder or clinical depression, it can lead to a variety of emotional and physical problems (Willner *et al.,* 2013). People who are depressed often have anxiety as well the two problems often occur together, and each can make the other worse. Feeling anxious makes the mind full of busy, repetitive thoughts, which make it hard to concentrate, relax, or sleep. People may have physical symptoms, such as headaches, aching muscles, sweating and dizziness. Anxiety may cause physical exhaustion and general ill health and sometimes accompanied with suicidal thoughts (Gotlib and Joormann, 2010 and Croy *et al.,* 2014).

Depression has been linked to problems or imbalances in the brain with regard to the Neurotransmitters Serotonin, Norepinephrine, and Dopamine. The evidence is somewhat indirect on these points because it is very difficult to actually measure the level of neurotransmitter in a brain. Antidepressant

medications which used to treat depression are known to act upon these particular neurotransmitters and their receptors (Porcelli *et al*., 2011).

Reserpine appears naturally in the dried roots of plants such as *Rauwolfia Serpentina* and *Vomitoria.* It is an indole alkaloid antipsychotic and antihypertensive drug that has been used for the control of high blood pressure and for the relief of psychotic symptoms (Dong *et al.,* 2009 and Ranganath *et al.,* 2013). The antihypertensive actions of Reserpine are a result of its ability to deplete catecholamines from peripheral sympathetic nerve endings. These substances are normally involved in controlling heart rate, force of cardiac contraction and peripheral resistance (Ranganath and Raj, 2015). After chronic administration of this drug some patients complained of major depression in 1950's (Lieth and Barrett, 1980). On the other hand, Henry *et al*. (1998) found that reserpine irreversibly blocks the intracellular vesicles monoamine transporters. This blockage overlap with the storage of monoamines into the intracellular vesicles, which effect in the depletion of catecholamines in nerve terminals and transient hypolocomotion and muscular rigidity.

The a ccumulation of neurotransmitters in the nerve terminal leads to a raise in the metabolism of these substances by monoamine oxidase. These can lead to the formation of reactive metabolites and hydrogen peroxide, producing free radicals and cellular damage by increased oxidative stress (albilio *et al*., 2003 and Bilska *et al.,* 2007).

The experiment was held to select the most suitable dose of reserpine for induction of depression in mice with minimal side effects and minimal mortality rate on mice in Egypt conditions.

MATERIAL AND METHODS

Animals: Animals used were sixty adult male albino mice weighing 20-25 g. purchased from National Research Centre (NRC, Cairo, Egypt). Upon arrival the animals were acclimatized for 7 days to a quiet colony room, with controlled ambient temperature (22 ±2 °C) and a 12 hour natural light/dark cycle, fed a standard diet and water was provided *ad libtum.*

Doses and injections: Reserpine was dissolved in glacial acetic acid and then diluted to a final concentration with distilled water, given to the mice at a single dose of 0.1, 0.5, 1 mg/ kg i.p of body weight according to Freitas *et al*. (2016) at the first day of the experiment.

Experimental design: The experiment divided into 4 groups 15 for each normal control, reserpine 0.1, 0.5 and 1 mg/kg. The mortality rate was recorded daily. All the groups injected intraperitoneal (i.p) a single dose of reserpine at the day 1, then forced swimming test was performed 1 hour later. The mice were left to rest at the second day and finally were sacrificed by decapitation at the 3rd day. The brain was excised and prepared for determination of Adenosine monophosphate (AMP) contents, adenosine Diphosphate (ADP) contents and Adenosine triphosphate (ATP) contenst, Monoamine neurotransmitters contents (Serotonin (5-HT), Norepinephrine (NE) and Dopamine (DA)), Malondialdehyde (MDA) contents, nitric oxide (NO) contents, Glutathione reduced (GSH) content , oxidized (GSSG) contents and 8- hydroxyl-2-deoxyguanosine (8-OHDG) contents.

Forced Swimming Test: Each mice was placed for 6 minutes in a cylindrical water tank (40 cm high, 40 cm diameter) where, water level was about 25 cm and water temperature was maintained at 23°C to 25°C. The total duration of immobility time and the Jumbing numbers of each animal in the last 4 minutes was recorded (Porsolt *et al.,* 1977).

Biochemical assays: Brain tissue was homogenized in 75% aqueous HPLC grade methanol (10% w/v). The homogenate was spun at 4000 r.p.m. for 15 minutes and the supernatant was isolated. The detection of Adenosinnes (AMP, ADP and ATP) by HPLC was done according to the method of Liu *et al*. (2006). Brain monoamines (5-HT, NE and DA) were detected by HPLC according to method described previously (Pagel *et al.,* 2000). Brain NO content was determined using HPLC according to Papadoyannis *et al.* (1999). The determination of MDA according to Ruiz-Larrea *et al.* (1994) and (GSH, GSSG) according to Bulaj *et al.* (1998) and Ellman (1959) by HPLC. 8-hydroxyl-2-deoxyguanosine (8-OHDG) Isolation and hydrolysis of brain 8-OHDG was performed as previously described (Lodovici *et al.,* 1997).

Statistical Analysis: Reported values represent means ± SE. Statistical analysis was evaluated by one -way ANOVA. Once a significant F test was obtained, LSD comparisons were performed to assess the significance of differences among various treatment groups. Statistical package for social science "SPSS" for Windows software, Release 18.0 (SPSS, Chicago, IL) was used at p value ≤ 0.05.

RESULTS

Mortality rate: The mortality percentage of groups given different doses of reserpine illustrated in Table 1 and Figure 1. It was clearly noticed that the mortality percentage is directly proportional to the increase in reserpine dose; the highest mortality percentage was in reserpine 1 mg followed by reserpine 0.5 mg and eventually reserpine 0.1 mg which recorded the lowest mortality rate compared to all other groups at p value ≤ 0.05.

Forced swimming test: Results of forced swimming test and number of jumping for groups of different doses of reserpine were shown in Figure 2 and Figure 3. Data revealed a significant increase at p value ≤ 0.05. The immobility time in all different reserpine doses 0.1 mg, 0.5 mg and 1 mg as compared to the control group. While a significant decrease was shown in all different doses groups in number of jumping when compared the control at p ≤ 0.05.

There was a significant decrease in groups treated with different doses of reserpine (0.1, 0.5 and 1mg/kg body weight) in ATP contents in brain areas while the cortex ADP and brain stem AMP contents were significantly increased as compared to the control group. More over the brain stem ADP contents in mice treated with 1 mg/kg showed a significant decrease in comparison with the control group. (P value ≤ 0.05) as shown in (Table 2).

It was noticed from Figure 4 and Figure 5 there was a significant decrease in different neurotransmitters content (cortex and brain stem 5-HT, NE and DA) in all reserpine treated groups in comparison with control group except brain stem NE in Res 0.5 group.

Concerning cortex and brain stem malondialdehyde (MDA) contents, there was a significant increase in MDA content in all reserpine groups when compared to the control group as shown in Table (3).

The data in Table 3 showed that there was a significant increase in cortex and brain stem, NO_2, NO_3 and NO in all reserpine administered mice with different doses (0.1, 0.5 and 1 mg/kg body weight) when compared to the control group except cortex NO_3 in Res 0.1 group wasn't significantly changed as compared to the control one.

There was a significant decrease in cortex and brain stem GSH and GSH/GSSG ratio. Values were reported in mice groups given different doses of reserpine in comparison to the control group (p value $\leq$ 0.05). On the contrary, there was a significant increase in cortex and brain stem GSSG in all groups given different doses in comparison with the control as showm in Table (3).

Statistical analysis of cortex and brain stem 8- hydroxyl-2-deoxyguanosine (8-OHDG) contents data of mice groups administered different doses of reserpine illustrated in Figure 6. There was a significant increase in cortex and brain stem 8-OHDG in all mice treated groups as compared to the control group at p $\leq$ 0.05.

DISCUSSION

The mortality rate of groups given different doses of reserpine showed the highest mortality rate was in 1mg/kg dose group while the moderate mortality was in 0.5 mg/kg dose group and the lowest mortality was in 0.1mg/kg dose group. It was clearly noticed that the mortality percentage is

dose dependent which means that death is directly proportional to the increase in reserpine dosage. The mechanism by which reserpine induce depression is related to depletion of CNS bioamine activity according to Tisdale and Miller (2010). The reserpine induced mortality may be attributed to severe depressive episodes associated with "high vulnerability period" during which depression increased risk of dying or having a life threatening physical conditions related to cardiovascular, respiratory or metabolic diseases like heart attacks and coronary diseases (European Society of Cardiology, 2015). Moreover, behavioral disturbances associated with depression including lack of self-care, loss of the will and motivation to live which result in severe infection, poor health and premature mortality. Rodents also share some of the factors that are influenced or altered by depression in humans, including changes in food consumption, sleep abnormalities and drug-withdrawal-induced anhedonia (Yankelevitch-Yahav et al., 2015).

In the present study, results of forced swimming test for groups of different doses of reserpine revealed significant decrease in immobility time in all different doses as compared to control group due to reserpine induced depression associated with despair and giving up and leave themselves to drowning. The result is in agreement with Huang et al. (2004); Arora and Chopra (2013) and Yankelevitch-Yahav et al. (2015). They noticed that the increase in immobility durations in the FST along with other physiological changes represented by prolonged monoamines depletion and oxidative stress. Foregoing investigations indicated that such physiological changes can persist for more than one week and thus the effectiveness of antidepressants

could be assigned by their capability to reverse the depressive-like effects of reserpine

In the same line Bolandghamat *et al.* (2011) studied depression model induced by reserpine in male wistar rats and recorded a significant increase in immobility time with forced swimming test in depressed rats. Several authors reported that the results from the forced swimming test could be related to the mood state of the animal and brain levels of noradrenaline, dopamine, serotonin and cholinergic neurotransmitters (Willner, 1984). These neurotransmitters are involved in the patho physiology of some types of depression and play a permissive role in the antidepressant activities (Willner, 1995 and Ferigolo *et al.*, 1998). The enhancement of serotonin, norepinephrine and dopamine content in the brain can reduce the immobility time of rats in the forced-swimming test (Cervo *et al*., 1990; Detke *et al*., 1995b and Calapai *et al.,* 2001). Enhancement of dopamine and norepinephrine neurotransmission may mediate climbing in the forced-swimming test (Cervo *et al*., 1992; Cabib *et al*., 1995 and Cryan *et al*., 2003).

The present study demonstrated that the cortex and brain stem content of the adenyl system compounds (AMP, ADP and ATP) of groups given different doses of reserpine (0.1, 0.5 and 1 mg/kg body weight) showed significant decrease when compared to the control group. These results are in agreement with Dias *et al* (2016).

Dunwiddie and Masino, (2001) investigated that the influence of reserpine upon tissue respiration and compared its effects with those of hydrallazine. A compound which interferes with cell metabolism may influence the high energy phosphate level, especially that of adenosine

triphosphate. Decreased ATP level may be an indicator for neurodegenerative disorder results in suppression of energy in the neurons (Darby *et al.,* 2003). Under physiological conditions, ATP is released in small amounts by astrocytes and neurons creating synaptic connections.

Reserpine is a monoamine depletor that blocks the vesicular monoamine transporter for neuronal transmission or storage, thus promoting oxidative catabolism by MAO (Lohr *et al.,* 2003); this makes its injection a reliable model of depression in rodents (Oe *et al.,* 2010). It's often said that depression results from a chemical imbalance, but that figure of speech doesn't capture how complex the disease is.

In the current study, there was a significant decrease in different neurotransmitters content (cortex and brain stem 5-HT, NE and DA and) in all reserpine treated groups in comparison with control group. Hall, (1998) reported that reserpine is a mono amines antagonist inducing depression to the extent that causes suicide, this theory called momoamine hypothesis. This result is coincide with Meyer *et al*. (2006) who stated studies of the neurobiological mechanism indicated the involvement of neurotransmitter systems in depression, showing abnormalities in the brain levels of 5-HT, NE, DA and their metabolites (Vines *et al*., 2012, Yu *et al*., 2013). The decreased brain content of 5-HT has been believed to be a core pathogenic factor in depression (Svenningsson *et al.,* 2006).

There is preliminary evidence that an increased availability of the brain monoamine oxidase, which metabolizes serotonin, may cause serotonin deficiency. In addition, loss-of-function mutations in the gene coding for the

brain-specific enzyme tryptophan hydroxylase-2 may explain the loss of serotonin production as a rare risk factor for depression (**Hasler, 2010).**

Concerning cortex and brain stem malondialdehyde (MDA) in the present study, there was a significant increase in MDA in all reserpine groups when compared to control group. In support of the present results, Chang *et al*. (2010) stated that increased MDA contents in depressed patients due to increased oxidative stress (Kurien and Scofield, 2006 and Mansour *et al.,* 2008).

Moreover, Michel *et al.* (2012) reported that modern imaging techniques show volume reduction of the hippocampus and the frontal cortex associated with depressive episodes. Cytochrome c release can increase free radical production by the mitochondrial electron transport chain causing non-specific cellular damage and necrotic-like morphology (Murphy *et al*., 1999). Depending on the levels of cytochrome c released by mitochondria, the amount of ATP may be insufficient to complete the apoptotic program. Because of this, cells can die by apoptosis or necrosis (Bonfoco *et al*., 1995). These results are in line with post-mortem studies of patients with depressive disorder. They point to a significant decrease of neuronal and glial cells in cortico-limbic regions which can be seen as a consequence of alterations in neuronal plasticity in this disorder. This could be triggered by an increase of free radicals which in turn eventually leads to cell death and consequently atrophy of vulnerable neuronal and glial cell population in these regions. Therefore, research on increased oxidative stress in unipolar depressive disorder, mediated by elevated concentrations of free radicals, has been undertaken.

In the present study, a significant decrease in cortex and brain stem glutathione (GSH) values and its oxidized form (GSSG) was reported in all groups given different doses of reserpine (0.1, 0.5 and 1 mg/kg body weight respectively) in comparison to control group. These results are parallel with Maes *et al*. (2011) who reported low level of glutathione and glutathione peroxidase associated with depression.

Glutathione it is a major endogenous free radical scavenger and its reduction can increase vulnerability to cellular oxidative stress (Berk *et al*., 2008). There is evidence that patients with depression have decreased antioxidant capacity in plasma as shown by lowered levels of glutathione peroxidase . Also a post-mortem study of prefrontal cortex in brain tissue, derived from the Stanley Foundation Consortium, found lowered levels of both GSH and GPX (Maes *et al.*, 2011).

Schulz *et al.* (2000) reported that there is significant evidence in the pathogenesis of several neurodegenerative diseases, including Parkinson's disease, depression, Alzheimer's disease, Friedreich's ataxia and amyotrophic lateral sclerosis, may involve the generation of reactive oxygen species and mitochondrial dysfunction. Also there is evidence for a disturbance of glutathione homeostasis that may either lead to or result from oxidative stress in neurodegenerative disorders (Halliwell, 2006 and Reynolds *et al*., 2007). Glutathione is an important intracellular antioxidant that protects against a variety of different antioxidant species. An important role for glutathione was proposed for the pathogenesis of Parkinson's disease, because a decrease in total glutathione concentrations in the substantia nigra has been observed in

preclinical stages (Gawryluk *et al*., 2011) at a time at which other biochemical changes are not yet detectable. Because glutathione does not cross the blood-brain barrier other treatment options to increase brain concentrations of glutathione including glutathione analogs, mimetics or precursors are discussed (Sting *et al.,* 2005).

There was a significant increase in cortex and brain stem NO_2, NO_3 and NO in all reserpine administered mice with different doses (0.1, 0.5 and 1 mg/kg body weight) compared to control group. The present finding is in agreement with Dhir and Kulkarni (2011) who reported that Nitric oxide has been known to play a significant role in the pathophysiology of various disorders of the body. Despite its very short half-life, nitric oxide is known to modulate various neurotransmitter system(s) in the body. It is speculated to play an imperative role in the pathogenesis of neurological disorders. This "wonder" molecule has been often found to possess a "dual role" in many neurological disorders of the body. Dysregulation of the nitrergic system has been well documented in depression (Bernstein *et al*., 2005; Kim *et al*., 2006 and Oliveira *et al*., 2008).

Evidences have shown its prominent role in the pathogenesis of major depression. Nitric oxide modulates norepinephrine, serotonin, dopamine, glutamate, the major neurotransmitters involved in the neurobiology of major depression. Accumulate Nitric oxide (NO) evidence supports the hypothesis that it plays a critical role in neuro-degenerative disorders (Bogdan, 2001).

Statistical analysis of cortex and brain stem 8- hydroxyl-2-deoxyguanosine (8-OHDG) data of mice groups administered different doses of reserpine revealed significant increase in cortex and brain stem (8-OHDG)

in mice groups administered with different doses of reserpine as compared to the control group. This result is coincide with Aitken and De Iuliis (2010) who reported that (8OHDG) formation and DNA fragmentation were highly correlated with each other and frequently associated with cell death. 8-hydroxyl-2-deoxyguanosine (8-OHDG) is a biomarker of systemic oxidative DNA damage and its level increased with clinical depression (Siyan *et al.,* 2012). The central nervous system is highly vulnerable to damage from oxidative stress; 8-hydroxylated guanine species such as 8-oxoguanine and 8-OHDG are repair products of oxidized guanine lesions. Previous studies linking increased concentrations of 8-OHDG to increased oxidative stress or disease states (Arnett *et al.,* 2005 and Arunachalam *et al.,* 2015)

Table (1): Showing mortality rate of mice groups (n=15) given different doses of reserpine:

Resepine Concentration	Number of Mice	Number of Survive Mice	Number of Mortality Mice	% of MortalityMice
Con	15	15	0	0%
Res 0.1	15	14	1	6.7%
Res 0.5	15	7	8	53.3%
Res 1	15	4	11	73.3%

Table (2): Showing cortex and brain stem Adinosine monophosphate (AMP) content, adenosine Diphosphate (ADP) content and Adenosine triphosphate (ATP) content, (ug/g) of different treated groups.

Brian area	Parameter Groups	AMP	ADP	ATP
Cortex	Control	7.199±0.452	10.53 ±0.596	31.317 ± 1.000
	Res 0.1	6.101±0.323 [a]	18.31 ± 0.138 [a]	17.03±0.300 [a]
	Res 0.5	6.146± 0.149 [a]	17.67±0.301 [a]	13.53 ±0.240[ab]
	Res 1	6.015± 0.242 [a]	11.32± 0.421[bc]	18.09±0.667 [ac]
Brain Stem	Control	9.432±0.276	17.57±0.563	30.39± 1.691
	Res 0.1	12.15±0.774 [a]	16.47±1.180	22.69±1.111 [a]
	Res 0.5	12.18± 0.625 [a]	16.08±0.583	17.65±1.363[ab]
	Res 1	12.49±0.347 [a]	15.20± 0.836 [a]	17.55± 0.557[ab]

Values are means of 8 mice ± SE at ($p < 0.05$), a=significant change from control, b= significant from Res 0.1 and c=significant from Res 0.5 mg/kg.
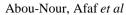
Table (3): Effect of different doses of reserpine on cortex and brain stem NO, (umole/g), MDA, (nmole/g), GSH, GSSG and GSH/GSSG ratio, (umole/g).

Brian area	Groups	Parameter						
		NO$_2$	NO$_3$	NO	MDA	GSH	GSSG	GSH/ GSSG
Cortex	Control	0.447± 0.036	0.147 ± 0.025	0.595± 0.055	14.51± 0.736	10.34± 0.239	0.558± 0.012	18.60± 0.68
	Res 0.1	0.833± 0.033 [a]	0.155± 0.021	0.988± 0.038 [a]	28.63± 0.343[a]	6.265± 0.299 [a]	1.048± 0.023[a]	6.00± 0.33 [a]
	Res 0.5	0.872± 0.030 [a]	0.239± 0.033[ab]	1.110± 0.030[ab]	30.24± 0.602[ab]	6.198± 0.335 [a]	1.786± 0.026[ab]	3.46± 0.16[ab]
	Res 1	0.899± 0.022[a]	0.250± 0.021[ab]	1.148± 0.033[ab]	29.72± 0.394[a]	6.261± 0.364[a]	1.664± 0.045[abc]	3.77± 0.22[ab]
Brain Stem	Control	0.762± 0.029	0.262± 0.021	1.025± 0.033	10.62± 0.074	21.45± 1.196	0.664± 0.039	32.30± 1.44
	Res 0.1	0.892± 0.038[a]	0.870± 0.037 [a]	1.763± 0.076 [a]	15.06± 0.258[a]	10.26± 0.524 [a]	1.421± 0.108[a]	7.51± 0.67[a]
	Res 0.5	0.897± 0.037 [a]	0.864± 0.048 [a]	1.736± 0.085 [a]	14.00± 0.597[ab]	23.71± 2.109 [b]	0.621± 0.033 [b]	38.85± 4.14[b]
	Res 1	0.902± 0.030 [a]	0.858± 0.032[a]	0.723± 0.066[a]	15.04± 0.344[ac]	22.54± 1.764[b]	0.611± 0.052[b]	37.36± 2.00[b]

Values are means of 8 mice ± SE at (P<0.05), a=significant change from control, b= significant from Res 0.1 and c=significant from Res 0.5 mg/kg.
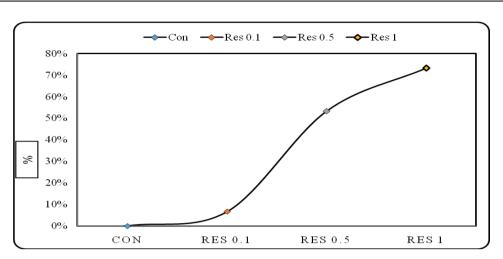
Figure (1): Showing mortality rate of mice groups given different doses of reserpine (0.1, 0.5 and 1 mg/kg). Values are means of 8 mice ± SE at ($P<0.05$).
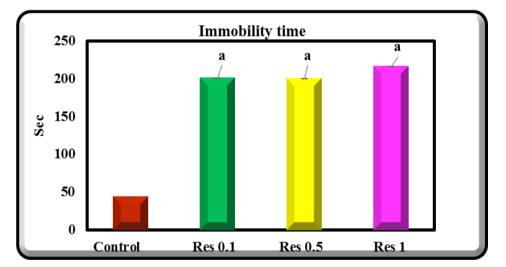

Figure (2): Showing immobility time (seconds) of groups treated with reserpine doses (0.1, 0.5, 1 mg/kg).Values are means of 8 mice ± SE at ($P<0.05$), a=significant change from control.
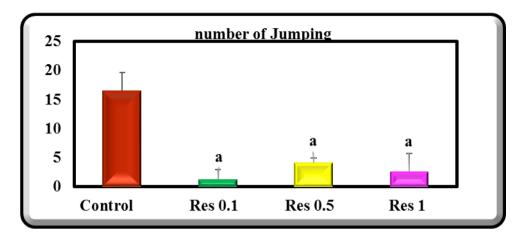
Figure (3): Showing number of Jumping of groups treated with reserpine doses (0.1, 0.5, 1 mg/kg). Values are means of 8 mice ± SE at (P<0.05), a=significant change from control.
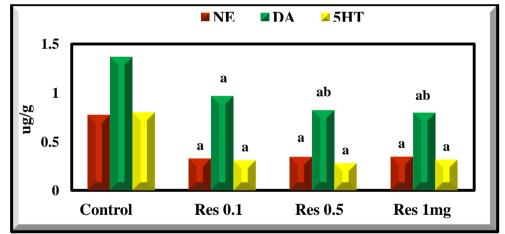

Figure (4): Effect of different doses of reserpine on cortex neurotransmitters (NE, DA and 5HT), (ug/g). Values are means of 8 mice ± SE at (P<0.05), a=significant change from control and b=significant from Res 0.1mg/kg.
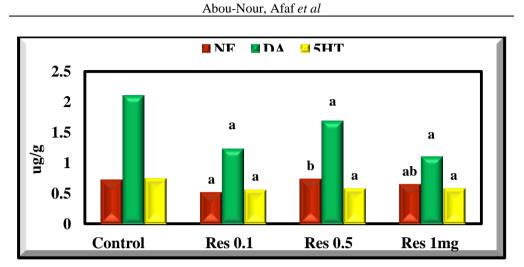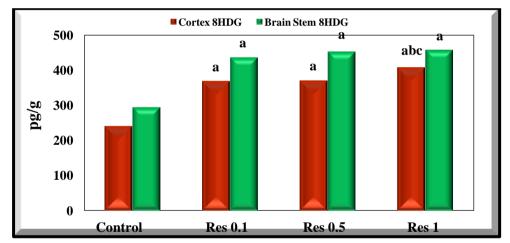
Figure (5): Effect of different doses of reserpine on brain stem neurotransmitters (NE, DA) and 5HT) (ug/g). Values are means of 8 mice ± SE at (P<0.05), a=significant change from control and b=significant from Res 0.1.

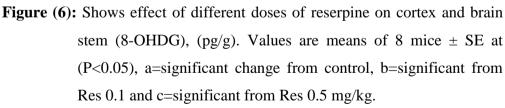**Figure (6):** Shows effect of different doses of reserpine on cortex and brain stem (8-OHDG), (pg/g). Values are means of 8 mice ± SE at (P<0.05), a=significant change from control, b=significant from Res 0.1 and c=significant from Res 0.5 mg/kg.

CONCLUSION

The present study suggested that the small used dose of reserpine (0.1 mg/kg) is the most suitable dose for induction of depression with the less mortality rate and the same effect on the brain monoamines contents.

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تحفيز النموذج الإكتئابى فى الفئران: الآثار المترتبة على الجرعات المختلفة للرزربين

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المستخلص

يعرف الاكتئاب باضطراب المزاج الذي تشمل خصائصه انخفاض الحركة بصورة دائمة وانخفاض قدرة تحفيز وبطء وظائف التفكير والإدراك. وقد أظهرت إحدى الدراسات المحلية أن معدل الانتحار بين الأشخاص الذين يعانون من الاكتئاب يقدر بـ 20 ضعفاً أعلى من نظيرتها لدى الأشخاص الطبيعيين. وقد تم إجراء هذه الدراسة بهدف تحديد الجرعة الأكثر ملاءمة من الرزربين لتحفيز الاكتئاب على الفئران مع أقل معدل للآثار الجانبية ومعدل الوفيات. وقد تم تحفيز الاكتئاب لدى الفئران عن طريق حقن جرعة مفردة من الرزربين داخل الصفاق (الغشاء البريتونى) وجرعات مختلفة بحجم (0.1، 0.5، و 1 ملجم / كلجم) في اليوم الأول، وتم إجراء اختبار السباحة القسري بعد مرور ساعة في اليوم الأول. وقد استغرقت التجربة يومين. وتم تسجيل معدل الوفيات. وتم استخراج المخ وتجهيزه لتحديد محتوى الأدينوسين أحادى الفوسفات، الأدينوسين ثنائي الفوسفات، الأدينوسين

ثلاثي الفوسفات، النواقل العصبية (السيرتونين، النورابينفرين والدوبامين)، المانوالدهيد، أكسيد النيتريك، الجلوتاثيون المنخفض، الجلوتاثيون المؤكسد و٨– هيدروكسيل–٢–دي أوكسي جوانوزين. وقد أظهر اختبار السباحة القسري وعدد القفزات عدم وجود فروق ذات دلالة إحصائية كبيرة بين الجرعات المختلفة للرزربين في حين كان معدل الوفيات متغيراً بشكل ملحوظ. وخلصت نتائج البحث إلى أن جرعة الرزربين الأكثر ملاءمة لإحداث الاكتئاب مع الحد الأدنى من الوفيات كانت ٠،١ ملجم / كجم من وزن الجسم.

الكلمات الدالة: الاكتئاب – الرزربين.