Medicine Updates

Faculty of medicine

April 2020,volume 1, issue 1

https://muj.journals.ekb.eg

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DOI:10.21608/muj.2020.15734.1000

ISSN : 2682-2741

Submitted: 6/8/2019

Accepted : 2/3/2020

Pages:1-8

The Effect of Amisulpride on Hippocampal Neurogenesis in an Experimental Model of Stressed Rats

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Abstract

Rationale: Amisulpride (**Sanofi**) is atypical antipsychotic against both positive and negative symptoms of schizophrenia . Efficacy is observed against negative symptoms in a low dose range of (50-300 mg / day) while in positive symptoms is observed in a high dose range (800-1200 mg / day) **Boyer et al , (1994**). It is a selective and potent antagonist at dopamine D2 and D3 receptors. Also it appears to have a useful potential for treatment of depression **Boyer et al ,(1999).**

Objectives

The current study investigated that amisulpride has antidepressant properties over a range of doses in two procedures namely the Forced Swim Test (FST) **Porso et al,(1978**) and immune-histopathology of Ki67. Also the effect of high versus low dose of amisulpride on hippocampal neurogenesis in male Wistar Han albino rats.

Methods

Sixty male albino wistar rats weighing about 150-200 gm are used in three main groups. Group I (n=12) were administered vehicle (saline) for 21 days , group II (n=12) exposed to forced swim test (FST) and vehicle (saline)for 21 days , group III(n=36) exposed to (FST) and amisulpride . The latter group was divided into three subgroups : IIIA (n=12) received 5mg /kg/day for 21 days, IIIB (n=12) received 10mg/kg/day for 21 days , IIIC (n=12) received 20mg/kg/day for 21days. The rats were observed for behavioural tests as immobility , climbing and swimming times. Then they were anaesthesized using urethane 1 gm/kg i.p **futterer CD, (2004),** then decapitated and the brains were quickly removed. Brain samples were placed in 10% formalin and were processed to form paraffin blocks. Half of them were used for biochemical analysis of BDNF levels in tissue and the other half were prepared and stained with Hematoxylin and eosin (H&E)stain and Immunohistochemical staining by Ki 67 (marker for proliferating cells).

Results

There is an increase of immobility time in seconds in CSS group compared with Control group with Mean ± SD (67.00±8.623 and 3.333±1.670 respectively) with P<0.0001 .While treating with oral amisulpride for 21 days in doses of 10mg/kg/day and 20mg/kg/day result in statistically significant decrease in immobility time as compared with CSS group with P value of< 0.0001 and F value of (4,54)=98.67. Amisulpride in 5 mg/kg was statistically insignificant.

Also there is a significant decrease in BDNF level in (pg/ml) in CSS group compared with Control group with Means±SD of (253.6±45.06and463.5±35.02 respectively) with P value of <0.0001 , while treatment with oral Amisulpride in 5, 10 and 20 mg/kg/day result in significantly statistically increase in BDNF value with Means±SD (420.5±29.84, 358.6±16.72and 400.6±18.18 respectively)with P values of <0.0001 and F(4,25) =1.276.

There is a significant statistical decrease in number of Ki-67 positive cells in SVZ in CSS group compared with control group with means (8.000 and 22.30 respectively) with P value of 0.0101 . Also treatment with oral Amisulpride 5 ,10 mg/kg/day result in insignificant increase in Ki-67 immunostained cells in

SVZ, with the maximum statistically increase with 20 mg/kg/day, with means (15.78,13.38 and 28.00 respectively)compared with CSS (Mean 8.000) with P values of 0.5108 ,0.8187and 0.0009 respectively and F (4,40)=6.628.

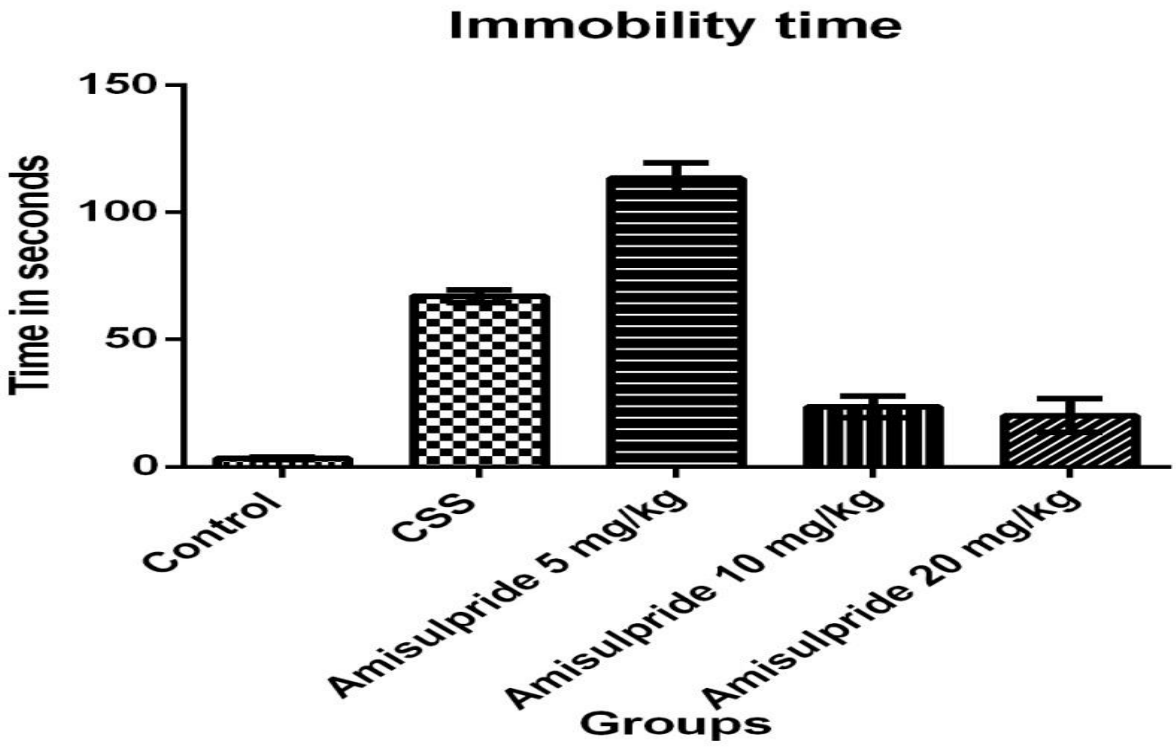
Behavioral results:

Table 1 showing difference in immobility time in seconds among different groups:

Groups of Rats (n= 12 Rats / group)	Immobility time in seconds (Mean ± SD)
Control	3.333±1.670
CSS	67.00±8.623
Amisulpride (5 mg/kg/ day)	113.4±21.09
Amisulpride (10 mg/kg/ day)	23.58±14.71
Amisulpride (20 mg/kg/ day)	20.09±22.18

Results are presented as Mean ± SD (n = 12 animals / group).

Fig 1 by using Graphpad prism :



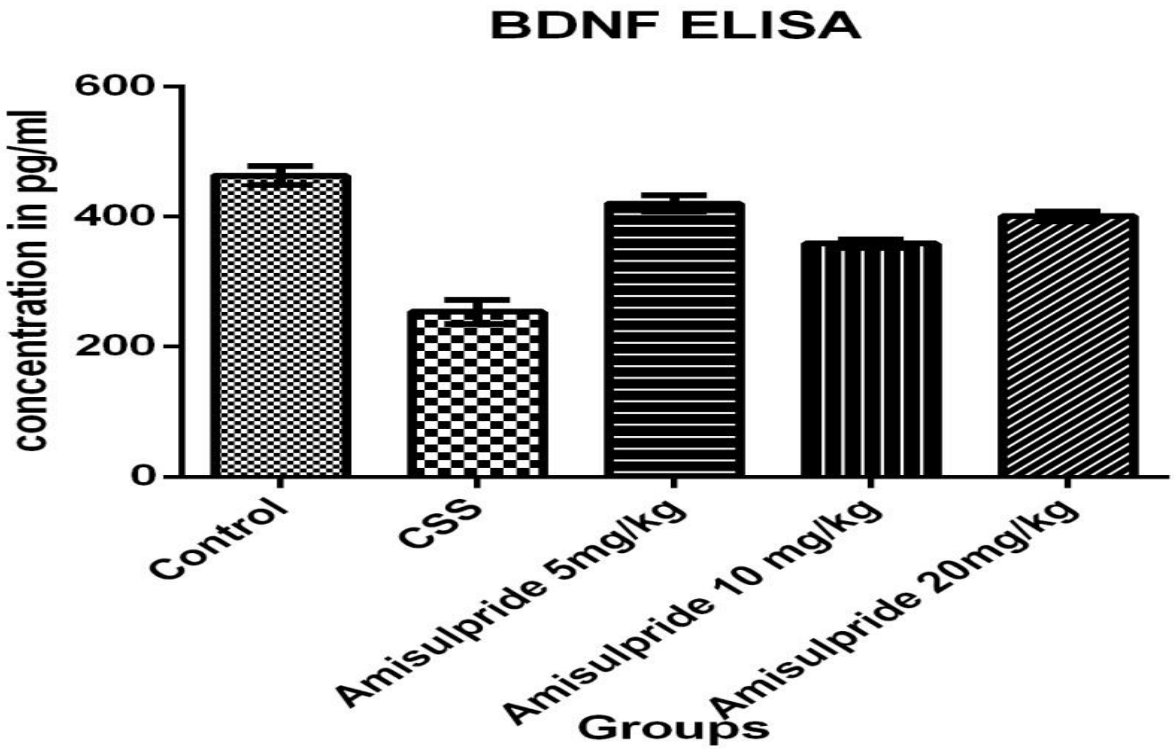
Biochemical results:

Table 2 showing difference in BDNF levels in (pg/ml)among groups:

Groups of Rats (n=12 Rats/group)	BDNF in (ng/ml) as Mean±SD
Control	463.5±35.02
CSS	253.6±45.06
Amisulpride (5mg/kg/day)	420.5±29.84
Amisulpride (10mg/kg/day)	358.6±16.72
Amisulpride (20mg/kg/day)	400.6±18.18

Results are presented as Mean ± SD (n=12 animals/group).

Fig 2: BDNF level



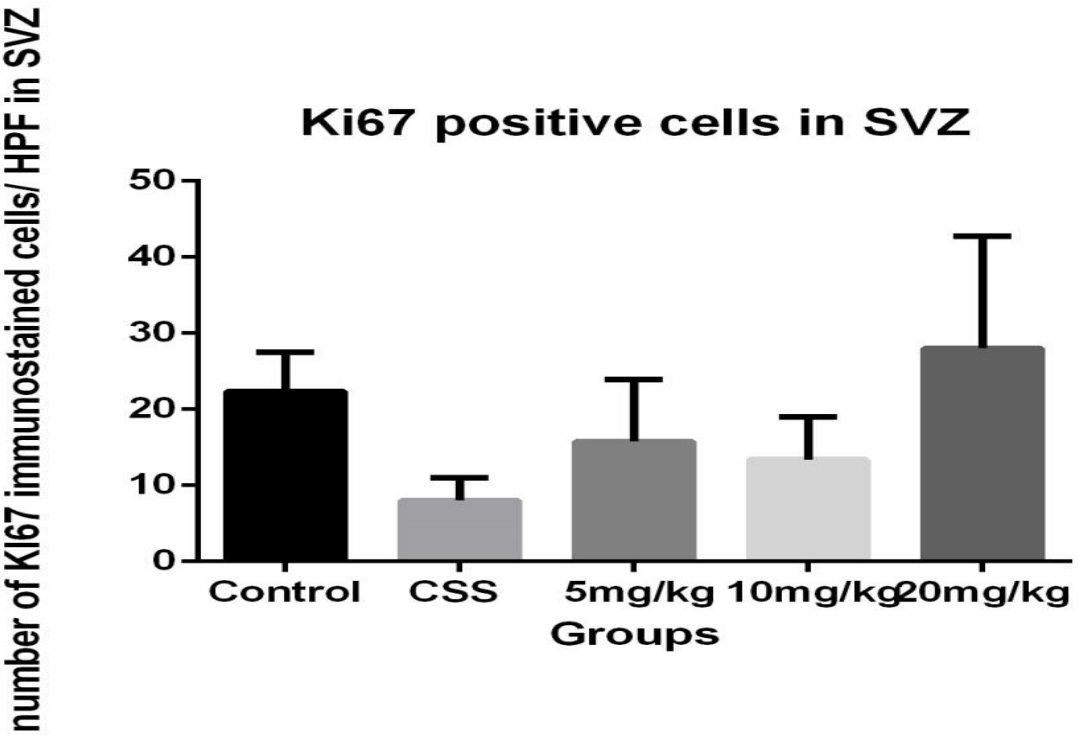
Histological results:

Table 3 showing number of Ki-67 immunostained cells/HPF in SVZ

Groups of Rats (n=12 Rats/group)	**Number of Ki-67 positive cells in SVZ (Mean±SD)**
Control	22.30±5.229
CSS	8.000±2.966
Amisulpride (5mg/kg/day)	15.78±8.136
Amisulpride (10mg/kg/day)	13.38±5.630
Amisulpride (20mg/kg/day)	28.00±14.75

Results are presented as Mean ± SD, n=12 animals /group.

Fig 3 Number of Ki-67 immunostained cells/HPF in SVZ.



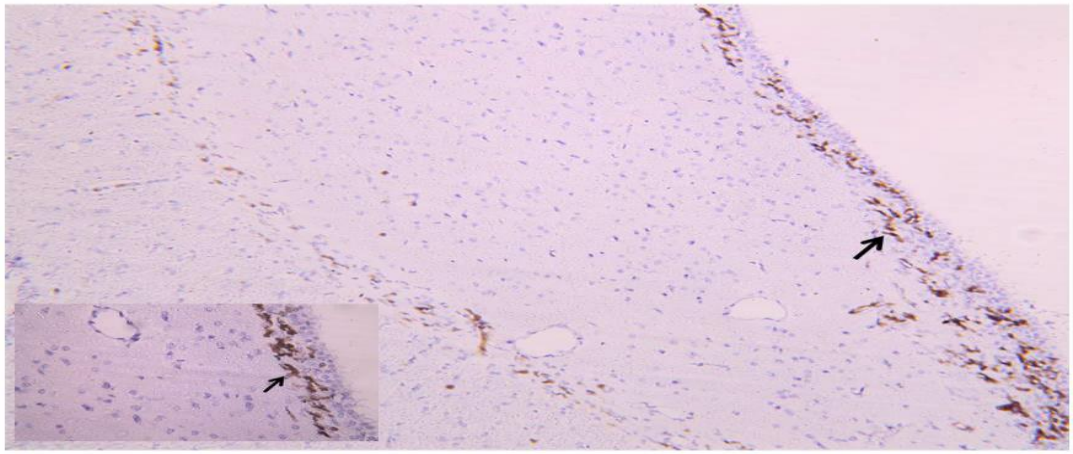


Fig 3 A: Micrograph showing immunohistochemistry of Ki-67 in SVZ (↑) in the control group (*100×, for inset 400×*).

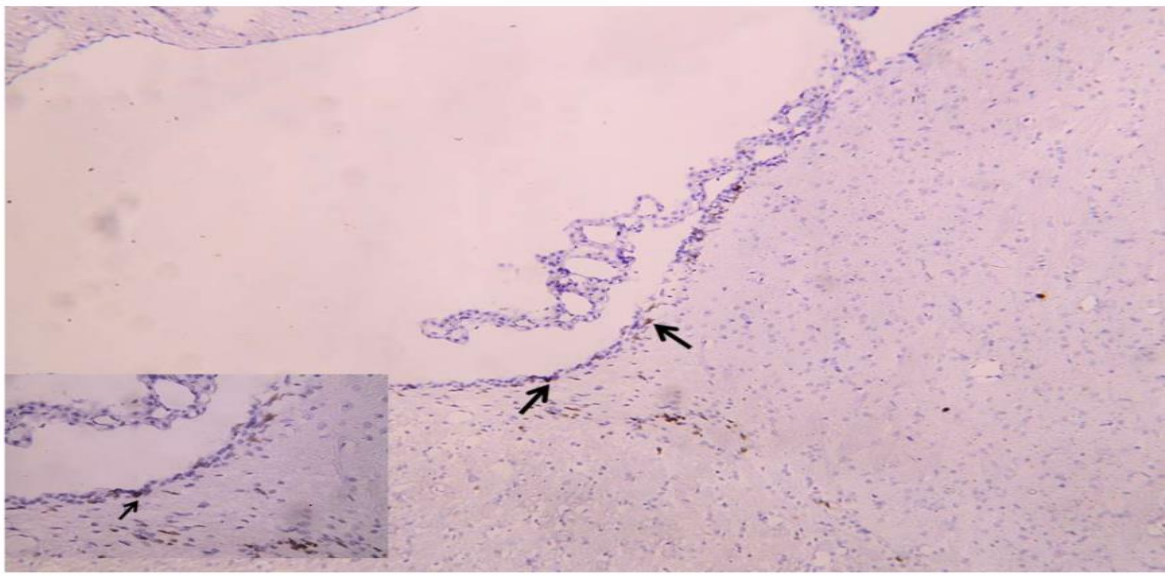


Fig 3 B : Micrograph showing immunohistochemistry of Ki-67 in SVZ (↑) in CSS group. A decrease in the number of Ki-67 positive cells is seen (*100×, for inset 400×*).

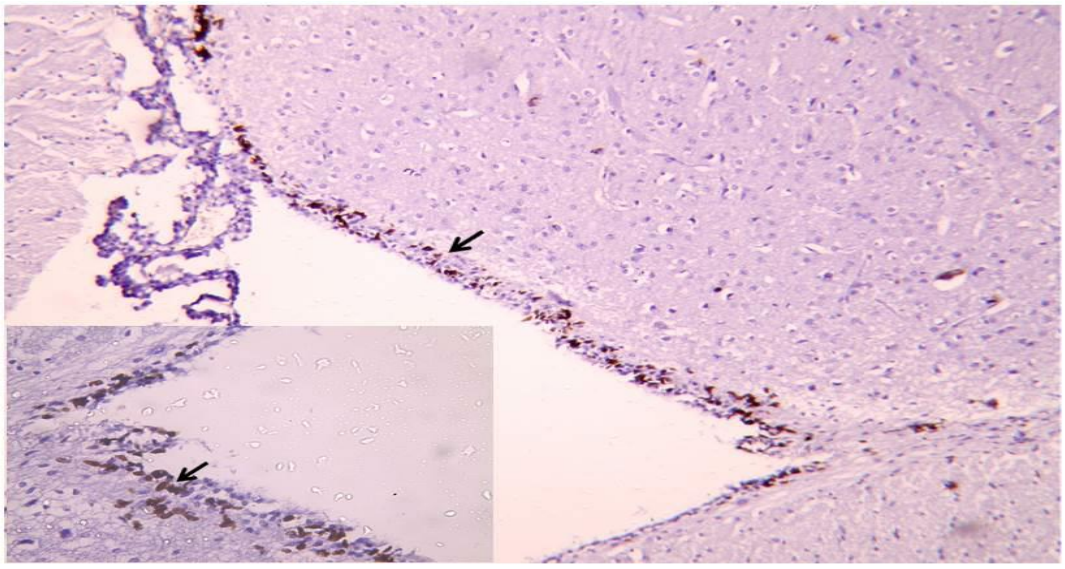


Fig 3 E : Micrograph showing immunohistochemistry of Ki-67 in SVZ (↑) in amisulpride 20 mg treated group. An apparent increase in Ki- 67 positive cells is seen (*100×, for inset 400×*).

Conclusion:

Amisulpride showed antidepressant effect over a ranger of doses as in 10 & 20mg/kg/day in addition to its antipsychotic effects. Moreover , the hippocampal neurogenesis may be altered in immunepsychiateric disorders like depression and neurodegenerative disorders.

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