Neurogenic and Behavioural Effects Induced by Duloxetine (Cymbalta) in Rats Exposed to Chronic Restraint Stress Model

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By

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Contents

Abstract

There is a growing evidence that increased neurogenesis and brain-derived neurotrophic factor (BDNF) can be relevant to mood disorders. The modulation of neurogenesis and BDNF biosynthesis following prolonged antidepressant treatment may contribute to neuroplastic changes required for behavioural response.

The objective of this study is to assess the behavioural and neurogenic effects of duloxetine on BDNF in the rat brain. Duloxetine was administrated in doses ١٠, ٢٠ and ٢٧ mg/kg/day. After ٢١ days, all rats were subjected to behavioural tests namely forced swimming test (FST) and open field test (OFT). Measurement of serum corticosterone level, brain derived neurotropic factor concentration in the prefrontal cortex and the hippocampus as well as histological study was carried out. The results showed that duloxetine (١٠, ٢٠ and ٢٧ mg/kg/day) produced a statistically significant *(p<٠,٠٠٠١)* reduction in the serum corticosterone concentration. Duloxetine in doses of ٢٠ and ٢٧ mg/kg/day produced a statistically significant *(p< ٠,٠٠١)* elevation of the BDNF concentration in the prefrontal cortex of the stressed rats while the elevation was statistically insignificant *(p>٠,٠٥)* with duloxetine in a dose of ١٠ mg/kg/day. Duloxetine in the three doses (١٠, ٢٠ and ٢٧

mg/kg/day) caused a statistically significant *(p< ٠,٠٥)* elevation of BDNF concentration in the hippocampus of the stressed rats. Moreover, duloxetine treated rats improved the stress-induced cellular changes. It also reversed the stress induced behavioural changes. Duloxetine induced a statistically significant reduction in the immobility time *(p< ٠,٠٠١)*, a statistically significant increase in swimming *(p< ٠,٠٠١)* and climbing time *(p< ٠,٠٠١)* in the FST. It also showed a statistically significant decrease in the frequency of rearing *(p< ٠,٠١)* and the number of total crossed squares *(p< ٠,٠٥)* in the OFT in the chronically stressed Wistar rats. Moreover, chronic duloxetine treatment showed a statistically significant positive correlation between the BDNF level in the PFC and the climbing time *(r^2= ٠,٤٧٤, p= ٠,٠٠٩)*.The BDNF level in the PFC and swimming time showed statistically significant negative correlation *(r^2= -٠,٤٤٥, p= ٠,٠١٦)*.

In conclusion, chronic duloxetine administration showed possible neurogenic effects on the rat prefrontal cortex and the hippocampus. This finding reflects an improved ability to cope under stressful conditions.

Keywords: Brain derived neurotrophic, duloxetine, chronic restraint stress, forced swimming test, open field test.

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List of Abbreviations

Abb.	Meaning
٥-HT	٥-hydroxy tryptamine
ADHD	Attention deficit hyperactivity disorders
BDNF	Brain derived neurotropic factor
BSA	Bovine serum albumin
CA	Cornu Ammonis
Cmax	Maximum plasma concentration
CORT	Corticosterone
CRS	Chronic restraint stress
CYP١A٢	Cytochrome P١A٢
CYP٢D٦	Cytochrome P٢D٦
CYP-٤٥٠	Cytochrome P٤٥٠
D.P.X.	Di-N- Butyl phthalate in Xylene
DPNP	Diabetic peripheral neuropathic pain
DSM IV-TR	Diagnostic statistical manual IV Text revised
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FST	Forced swimming test
GABA	Gama aminobutyric acid
GAD	Generalized anxiety disorder
GR	Glucocorticoid resceptors
HEPES	N-٢-Hydroxy Ethyl Piperazine–N`-٢-
HPA	Hypothalamic-pituitary-adrenal axis
HRP	Horseradish Peroxidase
ICD	International classification of disease