How Does Fluoxetine Influence the Social Interactions

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ABSTRACT
Exposure to continuous stress causes negative effects on mood and memory formation in hippocampus. Evidence suggesting that central nervous system γ-aminobutyric acid (GABA) concentrations are suppressed in major depressive disorder (MDD) has been reported since 1980. This concept is supported more recently by magnetic resonance spectroscopy data. These observations have compelled the researchers to preclude that MDD's underlying etiology is tied to an overall reduction in GABA mediated inhibitory neurotransmission. Fluoxetine influences various chemicals in the brain that when become unbalanced can cause depression, panic, anxiety, or obsessive-compulsive disorders. In this review, we discuss the connections between serotonergic and GABAergic neurotransmission under the influence of the selective serotonin reuptake inhibitor (SSRI) fluoxetine (PROZAC). The efficacy of SSRIs in the treatment of MDD is well established; however in long-term prevention of recurrence, their role remains unendorsed.

Keywords: Fluoxetine, long term follow-up, major depressive disorder, behavior medicine.

INTRODUCTION
In rats with auditory fear memory following fear conditioning, the study showed that the survival and number of new born cells that differentiated into mature neurons that are labeled by BrdU and NeuN decreased in the amygdala, but the increase in number of cells that developed into astrocytes labeled by BrdU and GFAP.¹ Fluoxetine was better effective than omeprazole for improving the symptoms of patients with heartburn and normal endoscopy who were not responding to single dose proton pump inhibitors (PPIs). This effect of fluoxetine was seen in those with normal esophageal pH rather than with abnormal pH.² Downregulation with needed modulation of the N-Methyl-D-Aspartate (NMDA) transmission was proposed to be essential mechanism of suppression of depression related behaviours by fluoxetine.³ Reduced brain arachidonic acid (ARA) metabolism in adult mice was reported after getting exposed to postnatal fluoxetine, with a 74% reduction in cytochrome P450 (CYP4A) protein in brain metabolism.⁴ Fetuses of rats receiving high doses of fluoxetine and olanzapine during the organogenesis period, showed cleft palate development, premature eyelid opening and torsion anomalies in the new born rats.⁵ Acute fluoxetine treatment increased plasma serotonin concentrations, thus promoting interactions between leukocyte and endothelial cells in-vivo. This indicates that serotonin is involved in acute inflammation.⁶ Selectivity of fluoxetine and nisoxetine, a selective structural congener of fluoxetine, was controlled by residues in different regions of the transporters, suggesting a complicated mechanism for selective recognition of structurally similar compounds in serotonin transporter (SERT) and nor epinephrine transporter.⁷ Calcium ions in cultured astrocytes exposed to the addition of KCl increased eventually in cultured astrocytes treated chronically with fluoxetine with the lag time until the effect was observed depending upon the fluoxetine concentration. This effect was stopped by nifedipine.⁸ Fluoxetine in juvenile monkeys upregulated SERT into young adulthood. Fluoxetine (FLX) had a good effect in the lateral temporal and cingulate cortices.⁹ CYP2C9 and CYP2D6 polymorphism have role in the clearance of FLX and in the stereoselective kinetic profiles of FLX enantiomers. Clear substrate inhibition was observed in the CYP2C9 wildtype and its
three variants mainly with R-FLX. Fluoxetine theoretically reduces axonal degeneration in multiple sclerosis by stimulating the energy metabolism through enhancing glycogenolysis, stimulating the production of brain-derived neurotrophic factor, and dilating the cerebral blood vessels. Under Fluoxetine, medial prefrontal cortex (mPFC) activation was upregulated and normalized in autism spectrum disorder (ASD) boys, but down regulated in Attention deficit hyperactivity disorder (ADHD) boys relative to placebo, which was concomitant with poor task performance in ADHD. Fluoxetine showed opposite effects on mPFC activation in ASD and ADHD during reversal learning, suggesting dissociated underlying serotonin abnormalities in the brain. FLX had no effect on the levels of serotonin, norepinephrine and their metabolites. But influenced dopaminergic activity. The study results showed that environmentally realistic concentrations of a single selective serotonin reuptake inhibitors (SSRI) significantly impairs the cryptic performances of newly hatched cuttlefish, and so reduce their chance for survival. Noted difference in treatment effects were observed between anxious dogs with aggression and anxious dogs without aggression. Positive correlations between owner compliance with the treatment plan and reported improvement were achieved during the study done on dogs with FLX.

Fluoxetine increases the susceptibility to predators and leads to a reduction in energy stores. Exposure to FLX in adolescence modulates responsiveness to emotional eliciting stimuli in adulthood, through longlasting adaptations in extracellular signal-regulated kinase (ERK)-related signaling within the ventral tegmental area (VTA). This study delineates the role played by ERK in regulating mood related behaviors in full lifespan. Medication naïve major depressive disorder (MDD) greatly decreased grey matter volume (GMV) in the right dorsolateral prefrontal cortex and left middle frontal gyrus as well as increased GMV in the left thalamus and right insula. Treating MDD had shown improvement of GMV in the left middle frontal gyrus and right orbitofrontal cortex. But no difference was noted in GMV between medication naïve MDD group and treated MDD group. The drug fluoxetine is present in the natural aquatic environment in ng/L intypical river concentrations. Past ecotoxicity studies assessed effects of this pharmaceutical on various aquatic species. Nanogram or picogram per litre concentrations are effective. Some other studies reported that have effects only if the water concentration is in the μg/L range. Risperidone (RIS) and FLX increased the extracellular level of cortical Dopamine (DA), serotonin (5-HT) and NA. Combined administration of both drugs was effective in enhancing DA release than when isolated administration of each of the drugs. Chronic escitalopram pretreatment attenuated the suppression in rapid eye movement sleep (REMS) due to SB-242084. But, the 5-hydroxytryptamine 2C (5-HT2C) receptor antagonist-induced elevations in passive wake and theta (5-9 Hz) power density during active wake and REMS were least affected by the SSRI. The sex difference in rats on the forced swim test without treatment and after fluoxetine, depends on the hormones organizational effects. In males, the response to FLX was based on organizational and activational actions.

**INTERACTIONS WITH CHEMICAL TRANSMITTERS IN BODY**

The levels of neurocan core protein, Rhodopsin and Arrestin were down regulated for the lower concentrations of fluoxetine suggesting potential changes in the phototransduction pathway. The expression of Rhodopsin1 tended to be enhanced for the lower concentration of sertraline. FLX reduced the health status of mussels and induced lysosomal alterations, as evidenced by reduction of lysosomal membrane stability

![Fig. 1: Therapeutic perspectives for Fluoxetine](image-url)
in haemocytes and by lysosomal accumulation of neutral lipids in digestive glands. Antioxidant responses to FLX were not detected in digestive gland. Increase of catalase and glutathione-s-transferase activities were seen in gills with decrease of acetylcholinesterase activity.\textsuperscript{23} Deficits in pretreatment gamma-aminobutyric acid-B (GABAB), were related to fluoxetine nonresponse in the depressed youth. Prior research demonstrated that GABAB interneurons had serotonergic input and antidepressants modulated GABAB receptors.\textsuperscript{24} Diet with out omega-3 fatty acid precursor alpha-linolenic acid (DEF) + chronic fluoxetine (FLX) treatment rats exhibited greater midbrain, and lower frontal cortex, 5-HT1A mRNA expression compared with all groups including diets with omega-3 fatty acid precursor alpha-linolenic acid (CON) + FLX rats. DEF + FLX rats showed higher midbrain alpha2A adrenergic receptor mRNA expression which was positively correlated with climbing behavior in the forced swimming test (FST).\textsuperscript{25} Treatment with placebo showed an unusual high response rate in children with anxiety disorders. Clomipramine showed efficacy same compared with fluoxetine, it was not superior to placebo.\textsuperscript{26} In a study done on patients with recurrent major depressive disorder (MDD), treatment outcomes with venlafaxine extended release and fluoxetine showed no difference in the basis of sex or menopausal status.\textsuperscript{27} No changes were observed in cell-free haemolymph lysozyme activity, whereas gill acetylcholinesterase (AChE) activity decreased significantly in clams exposed to 1 or 5 μg l(-1). The study findings showed that fluoxetine significantly affected immune parameters and AChE activity in clams.\textsuperscript{28} Study done by Lee et al, (2013) suggests that the neuroprotective effect of fluoxetine was mediated by blocking matrix metalloproteases activation followed blood brain barrier (BBB) disruption after transient global ischemia. FLX is a potential therapeutic agent for preserving BBB integrity following ischemic brain injury in humans.\textsuperscript{29}

### ROLE OF SEROTONIN

The study findings showed serotonin 2 receptors had influence in the development of perturbed emotionality following postnatal fluoxetine. The altered balance of signaling through 5-HT1A and 5-HT2A/C receptors in early life affects the anxiety behavior.\textsuperscript{30} In a 25-year-old Caucasian woman with type 1 diabetes mellitus, the reduced insulin requirements continued during the period of fluoxetine treatment while glycated hemoglobin levels were not changed.\textsuperscript{31} After 4-weeks of being treated with fluoxetine, a selective serotonin reuptake inhibitor ameliorated the chronic mild stress (CMS) affected risk assessment behaviors, and also restored the CMS impaired correlations between risk assessment and decision making related action selection.\textsuperscript{32} Antidepressant efficacy of short-term therapy with saffron capsules was same compared with fluoxetine in patients with a prior history of percutaneous coronary intervention, who were suffering from depression.\textsuperscript{33} Study results revealed that the depletion and the blockage of 5-HT modifies subthalamic nucleus (STN) neuron firing pattern. STN neuron activity is influenced by 5-HT1A and 5-HT2C receptors located inside as well as outside the STN. FLX increased the STN neuron activity in chronically FLX treated rats.\textsuperscript{34} Chronic treatment with fluoxetine through the drinking water route, normalized GABA release and improved the recovery of spatial memory abilities, spatial working memory for alternation, and hippocampal synaptic plasticity in adult mice model of Down’s syndrome.\textsuperscript{35} One theory of inefficacy of FLX is that underweight patients do not have the nutrients required to make serotonin, therefore preventing SSRI from getting into action. Another theory implicated the dysregulation of the serotonin receptor. Despite the lack of evidence, FLX’s useful in certain underweight and weight-restored patients.\textsuperscript{36} FLX intercepts the bacterial lipopolysaccharide (LPS) induced decreases in intracellular AChE-S. AChE-S interacts with the nuclear factor kappa B (NFkB)-activating intracellular receptor for activated C kinase (RACK1). This prevents NFkB activation by residual RACK1 and its interacting protein kinase PKCβII. The research study findings attributed the anti-inflammatory properties of SSRIs to surface membrane interference with leukocyte TLR4 activation associated with intracellular limitation of pathogen-inducible changes in AChE-S, RACK1, and PKCβII.\textsuperscript{37} Research study indicated that early FLX exposure in non human animals alters the development of the brain in methods related to

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**Fig. 2: Commonly used SSRIs**

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behaviour in adulthood, decreasing exploration and social interaction, and altering anxiety or depression behaviours. Overexpression of calmodulin-dependent protein kinase II (CaMKII) in nucleus accumbens (NAC) reduces antidepressant effects of FLX in the chronic social defeat paradigm. Inhibition of CaMKII activity in NAC mimics fluoxetine exposure. The study results suggest that epigenetic suppression of CaMKII expression in NAC is behaviorally related and proposes new pathway for therapeutic intervention in depression and related syndromes. The study done by immunofluorescence analysis for perineuronal nets (PNNs) indicated that FLX decreases the levels of parvalbumin, a mature marker of fastspiking interneurons, and PNNs in parvalbumin+ interneurons in the medial frontal cortex. This suggests that FLX treatment induces a dematuration of these neurons. Induction of a juvenile-like state in fastspiking inhibitory interneurons was involved in the therapeutic mechanism of FLX or some of its adverse effects. Fluoxetine and pergolide enhanced the expression levels of mRNAs for glucose transporter 1 (GLUT1) and GLUT10 in the mice brain. The expression of GLUT6 in tissue was increased by administering pergolide. In contrary, fluoxetine and pergolide had no effect on the expression levels of mRNAs for the other GLUTs and sodium dependant transporter1. Causation and social or some of its adverse effects.

CONCLUSION

Studies using immunostaining with occludin antibody showed fluoxetine preserved the integrity of vascular networks in hippocampal areas after injury. Fluoxetine prevents the infiltration of macrophages thus inhibiting the mRNA expression of inflammatory mediators due to injury. Prozac is one antidepressant that has been approved for the treatment of depression in young adults. Fluoxetine inhibits several isozymes of the cytochrome P450 system which involve in drug metabolism. Its effect on dopamine and norepinephrine forms the back bone for antidepressant action. Fluoxetine delays the reuptake of the neurotransmitter lowered in depressive persons i.e., serotonin, making to persist longer duration after being released from the neurons, thus improving their social interactions.

REFERENCES


22. da Costa CZ and de Morais RM. J Child AdolescPsychopharmacol. 2013 Dec;23(10):687-92. doi:
Comparison among clomipramine, fluoxetine, and placebo for the treatment of anxiety disorders in children and adolescents.


