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EFFECT OF SUB-ACUTE ADMINISTRATION OF CELECOXIB ON ANTIDEPRESSANT EFFECT OF FLUOXETINE IN ALBINO MICE

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ABSTRACT

Depression has recently been shown to have an inflammatory component. Celecoxib, a selective COX-2 inhibitor, inhibits the production of prostaglandins and proinflammatory cytokines and also increases tryptophan levels and serotonin availability in depressed patients. Selective serotonin reuptake inhibitors (SSRIs) like fluoxetine are effective antidepressants, but their efficacy decreased in the presence of non-steroidal anti-inflammatory drugs (NSAIDs) in some studies. Other studies have shown that there is an increase in antidepressant activity of fluoxetine when celecoxib is co-administered. Hence, we wanted to evaluate the effect of sub-acute administration of celecoxib on antidepressant activity of fluoxetine in albino mice. After clearance from Institutional Animal Ethics Committee, 24 healthy albino mice (20 - 30g) of either sex were divided into four groups of six mice each and administered Distilled water (control), Fluoxetine 5mg/kg (standard), Fluoxetine 5mg/kg + Ibuprofen 100mg/kg and Fluoxetine 5mg/kg + Celecoxib 5mg/kg respectively by intraperitoneal route for 21 days. Testing for antidepressant effect was done by Tail Suspension Test (TST) and Forced Swim Test (FST) in all groups at baseline (Day 0) and Day 21. Cumulative duration of immobility (which is indicative of antidepressant activity) within a 5 minute testing period was measured (in seconds) in all groups and the results were expressed as Mean ± SD. Statistical analysis was done by one-way ANOVA followed by Unpaired 't' test with $P<0.05$ as the level of significance (95% confidence limits). Cumulative duration of immobility (in seconds) within a 5 minute testing period was significantly decreased after drug administration in fluoxetine group in the FST and TST, compared to normal control. Duration of immobility however significantly increased in both groups wherein ibuprofen and celecoxib were added to fluoxetine in both TST and FST. Thus, acute and sub-acute administration of celecoxib for 21 days significantly decreased the antidepressant effect of fluoxetine in albino mice.

KEY WORDS: **Antidepressant, Celecoxib, Fluoxetine, FST, TST**

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INTRODUCTION

Depression is an affective disorder characterized primarily by change of mood with common clinical features like sad mood, loss of interest and pleasure, low energy, worthlessness, guilt, psychomotor retardation or agitation, change in appetite and sleep, melancholia, suicidal thoughts etc. It is associated with significant morbidity and mortality and interferes with everyday life for prolonged periods.[1]Depression is the fourth leading cause of disability and disease worldwide. World health organization (WHO) projections indicate that depression will be the highest ranked cause of disease burden in developed countries by the year 2020.[2] Inflammation is a complex reaction in tissues that consists mainly of responses of blood vessels and leukocytes.[3] The inflammatory process is the response to an injurious stimulus, evoked by various noxious agents and the ability to mount an inflammatory response is essential for survival. However, in some situations, the inflammatory response may be exaggerated and sustained without any apparent benefit and even with severe adverse consequences.[4] In such cases, non-steroidal anti-inflammatory drugs (NSAIDs) which act by inhibiting cyclo-oxygenase (COX) and thereby, decrease prostaglandin synthesis, may be used to treat inflammation. Ibuprofen is a non-selective COX inhibitor whereas celecoxib is a selective COX-2 inhibitor. Selective COX-2 inhibitors cause less gastrointestinal adverse effects than non-selective COX-inhibitors. However, there is an increased risk of myocardial infarction and stroke with selective COX-2 inhibitors, hence these drugs should never be used as first choice NSAIDs. If and when used, it should be for the lowest possible dose and shortest duration. Celecoxib is approved in the US for management of acute pain in adults, treatment of osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis and primary dysmenorrhoea.[4] The etiology of depression remains unclear, but growing evidence suggests that immune dysregulation and inflammation may be involved in depressive disorders.[5] Thus, it is probable that COX enzyme is upregulated in depressive states, leading to pro-inflammatory processes in the CNS.Selective Serotonin reuptake inhibitors (SSRIs) are widely used clinically for antidepressant activity. Non-selective COX-inhibitors – ibuprofen, naproxen and aspirin have been shown to reduce the antidepressant activity of SSRIs – citalopram, fluoxetine as well as other antidepressants – desipramine, imipramine and bupropion.[6] However, no selective COX-2 inhibitor was tested. On the other hand, there are studies which have demonstrated enhanced efficacy of fluoxetine when selective COX-2 inhibitors were given concurrently in both animals[7] and humans.[8] In this background, we wanted to evaluate the effect of concurrent sub-acute administration of fluoxetine and celecoxib in animal models of depression. Our objective was:

- To evaluate the effect of sub-acute administration of celecoxib on the antidepressant activity of fluoxetine in albino mice.

MATERIALS AND METHODS

We performed the following experiments after obtaining clearance from the Institutional Animal Ethics Committee.

Experimental animals

We obtained twenty four healthy adult albino mice of either sex (20-40g) from the Central Animal House of our institute and kept them for one week in the departmental animal house, grouped in separate cages. We ensured maintenance of 12 hours light:dark cycle and free access to laboratory diet and water, as per the recommendations of the Committee for the purpose of control and supervision of experiments on animals (CPCSEA).[9]

Drugs and doses

We acquired the following drugs – fluoxetine, ibuprofen and celecoxib from Cadila

Pharmaceuticals Ltd., J&K, Abbott India Ltd., Goa and Zydus Cadila, Zydus Healthcare, Sikkim respectively. We selected low doses of fluoxetine and celecoxib and standard dose of ibuprofen from previous studies.[10-12] We suspended the drugs in Distilled water (D/W) (1ml/kg) and administered Fluoxetine 5mg/kg, Ibuprofen 100mg/kg and Celecoxib 5mg/kg intra-peritoneally.

Grouping and treatment scheduling

We divided healthy albino mice of either sex (20-40g) into four arms containing six mice each for testing antidepressant activity (n=24). The treatment schedule was as follows:

Group A: D/W (1ml/kg)
Group B: Fluoxetine (5mg/kg)
Group C: Fluoxetine (5mg/kg) + Ibuprofen (100mg/kg) administered separately
Group D: Fluoxetine (5mg/kg) + Celecoxib (5mg/kg) administered separately

We administered daily doses of the drugs for 21 days.

Experimental Design

We used the standard Behavioural Despair Models for evaluating antidepressant effect - Tail suspension test (TST) and Forced Swim Test (FST). After taking baseline values of TST and FST on Day 0, we administered the vehicle and the drugs intra-peritoneally for 21 days. Then, we repeated TST and FST on Day 21.

TST

TST is a simple, rapid and reliable method to screen antidepressants and other class of psychotropics, which was first proposed by Steru, *et al*.[13] In this test, we suspended a mouse by the tail using adhesive tape from a horizontal bar 50cm above the ground. It initially tried to escape its situation by displaying twisting movements. Gradually, it developed 'behavioural despair' - alternate agitation and immobility which is indicative of a state of depression. Antidepressants are expected to reduce the immobility (state of depression) that mice display after active and unsuccessful attempts to escape when suspended by the tail.We recorded the total duration of immobility (in seconds) during a five minute testing period using a stop watch. On Day 21, we treated the groups of animals with the test compounds or the control/vehicle one hour prior to testing.

FST

The FST also predicts antidepressant activity in rodents and was first described by Porsolt, *et al*.[14] We conducted a pre-test session wherein the naïve mice had to swim for 15 minutes inside a vertical plastic cylinder (height: 30 cm; diameter: 15 cm, containing 15 cm of water at room temperature). Mice placed in the cylinders for the first time were initially highly active, but after some time, their activity decreased and became interspersed with phases of immobility or floating of increasing duration. An animal was regarded as immobile whenever it remained floating passively in the water in a slightly hunched but upright position, its nose just above the surface. After five to six minutes, immobility reached a plateau where the mice remained immobile most of the time. After 15 minutes in the water, we removed and dried them and wrapped them with soft towels.

We tested them again 24 hours later and measured the total duration of immobility during a five minute period for baseline (Day 0) values. On Day 21, we administered the drugs/control one hour prior to testing. We recorded the duration of immobility during the five minute observation period for all mice in each group. The immobility exhibited by rodents when they are placed in an inescapable cylinder of water reflects the cessation of persistent escape-directed behavior and antidepressant drugs reduce duration of immobility (depression).

Statistical analysis

We performed Statistical analysis, using SPSS statistical software Version 16.0. Duration of immobility was expressed as Mean ± SD. For demonstration of antidepressant activity, we used one way ANOVA, followed by Unpaired 't' test for analysing the difference between groups (if any), with $P < 0.05$ as level of significance with 95% confidence interval.

RESULTS

The results of TST and FST expressed as Mean ± SD are shown in Table 1 and results of one way ANOVA are shown in Table 2. Inter-group comparisons on day of experiment (Day 21) using Unpaired 't' test are shown in Tables 3 and 4.

Table 1

Cumulative duration of immobility (seconds) in Tail suspension test (TST) and Forced swim test (FST), expressed as Mean ± SD

GROUP	TST (D0)	TST (D21)	FST (D0)	FST (D21)
A	176.17 ± 33.41	168.67 ± 24.10	195.17±21.84	161.50 ± 1.97
B	137.67 ± 33.83	83.00 ± 12.33	159.33±14.75	134.00 ± 4.54
C	184.50 ± 32.76	205.00 ± 29.66	183.00±8.94	195.50 ± 15.54
D	145.83 ± 30.73	184.17 ± 16.56	175.83±42.24	232.50 ± 19.69

Table 2

Results of one way ANOVA on D0 (baseline) versus D21 (post-drug/control)

TST D0	0.060 (Not significant)
FST D0	0.132 (Not significant)
TST D21	0.000 (Highly significant)
FST D21	0.000 (Highly significant)

Table 3

Results of Unpaired 't' test between groups on day of experiment (Day 21) for TST

Group		A	B	C	D
A	t-test				
	P-value				
B	t-test	7.752			
	P-value	0.000**			
C	t-test	2.329	9.302		
	P-value	0.042	0.000**		
D	t-test	1.299	12.004	1.502	
	P-value	0.223	0.000**	0.164	

indicates significant and ** indicates highly significant difference between groups

Table 4

Results of Unpaired 't' test between groups on day of experiment (Day 21) for FST

Group		A	B	C	D
A	t-test				
	P-value				
B	t-test	6.024			
	P-value	0.000**			
C	t-test	5.316	2.269		
	P-value	0.000**	0.047*		
D	t-test	8.791	6.183	3.614	
	P-value	0.000**	0.000**	0.005**	

indicates significant and ** indicates highly significant difference between groups

DISCUSSION

Our objective was to evaluate the effect of concurrent administration of celecoxib on the antidepressant effect of fluoxetine in albino mice over a period of 21 days, using behavioural despair models of depression.In both TST and FST, there was a mean decrease in duration of immobility from baseline values following drug administration in fluoxetine group. But, an increase in mean duration of immobility was seen in combination groups of fluoxetine with ibuprofen and with celecoxib. Thus, administration of drugs in the combination groups increased the baseline parameter, that is, cumulative duration of immobility (in seconds) in TST and FST. Therefore, we observed a decrease in the antidepressant activity when the anti-inflammatory drugs ibuprofen or celecoxib were given concurrently with fluoxetine.Results of one way ANOVA revealed no significant difference between the performances of the groups in TST and FST on Day 0, indicating that the groups were comparable at baseline. But, we observed a highly significant difference (P<0.000) between the performances of the animals in both TST and FST on Day 21.On comparing the performance of the drug treated groups in TST and FST on Day 21, fluoxetine + ibuprofen and fluoxetine + celecoxib combination groups showed highly significant decrease in antidepressant activity respectively compared to fluoxetine alone. There was no significant difference between the combination groups in TST, but we observed a highly significant difference between fluoxetine and ibuprofen versus fluoxetine and celecoxib group in FST. Thus, sub-acute administration of fluoxetine with ibuprofen and with celecoxib probably reversed the significant antidepressant activity which was seen after administration of fluoxetine alone. In an earlier study, ibuprofen similarly decreased the antidepressant activity of fluoxetine.[6] But, reduction of antidepressant activity of fluoxetine, which we observed with concurrent administration of celecoxib, contrasts with earlier reports of enhanced antidepressant activity with such combination both in animals and humans.[7,8]The neuropathology of depression has recently been reported to be closely associated with neuroinflammation. Microglia play a role in innate immunity in the CNS and may contribute directly to the neuroinflammation by producing various pro-inflammatory cytokines and free radicals. These substances cause the synaptic pathology, a decrease in neurogenesis, and white matter abnormalities found in the brains of depressed patients.[15] In another study, elevations in pro-inflammatory cytokines and other inflammation-related proteins were found in plasma and cerebrospinal fluid of patients with major depression. Elevated levels of pro-inflammatory cytokines persist after clinical symptoms of depression are in remission and can also predict the onset of a depressive episode.[16] According to Krause, *et al*, immune activation induces a pro-inflammatory state, which enhances the tryptophan degradation into kynurenine as shown in patients with major depression.[17] In a recent report, Maes, *et al* states that depression is characterized by aberrations in inflammatory pathways, activation of cell-mediated immune pathways, elevated pro-oxidative processes, lowered levels of key antioxidants, damage to mitochondria and mitochondrial DNA and progressive neurodegeneration, reduced neurogenesis and neuronal plasticity.[18] Thus, there is clear evidence for the “cytokine hypothesis” of depression.[6]

Elevated levels of inflammatory cytokines in major depressive disorder (MDD) could be due to brain dysfunction (which should reduce with antidepressant treatment) or, they could contribute to depressive symptoms in MDD.[19] In this light, many researchers have tried to find out whether antidepressants decrease or modulate the inflammatory processes that are activated in depression. According to Maes, *et al*, antidepressants tend to normalize the abnormalities in various immune related pathways which occur in depression.[18] Monji, *et al* have shown the inhibitory effects of some antidepressants on the release of inflammatory

cytokines and free radicals from activated microglia[15] Antidepressant treatment can lead to a normalization of elevated cytokine levels in major depression.[16] In one study, the inflammatory markers - C-reactive protein (CRP) and IL-6 were increased in men using serotonin-norepinephrine reuptake inhibitors (SNRI) and CRP alone was raised in men and women using tri- or tetracyclic antidepressants, but IL-6 decreased among men using SSRIs. Thus, specific antidepressants may differ in their effects on inflammation.[5] The strength of this statement is enhanced in one meta-analysis of human studies on the effect of antidepressant medication treatment on serum levels of inflammatory cytokines. Here, the researchers found that overall, while antidepressant treatment reduced depressive symptoms, it did not reduce serum levels of TNF*α*. On the other hand, antidepressant treatment did reduce levels of IL-1*β* and possibly those of IL-6. Serotonin reuptake inhibitors possibly reduced levels of IL-6 and TNF*α*, but other antidepressants did not reduce cytokine levels.[19] NSAIDs can interfere with the effects of antidepressants.[16] In one study, the effects of anti-inflammatory medication and antidepressants on cytokines in blood culture with immune challenge, using bacterial mimetic lipopolysaccharide (LPS) were investigated. Stimulation with LPS induced increased production of pro-inflammatory and anti-inflammatory cytokines. Celecoxib was beneficial in terms of re-balancing the immune function, but not in re-balancing neuroactive metabolites.[17] In another study, the researchers investigated a possible interaction between antidepressant agents and NSAIDs on antidepressant-induced behaviours and on p11, a biochemical marker of depressive-like states and antidepressant responses. After administering NSAIDs and antidepressants in drinking water orally for 14 days, they tested for antidepressant activity. They found that frontal cortical levels of certain cytokines (e.g., TNFα and IFNγ) were increased by serotonergic antidepressants, which in turn increase p11 levels in the forebrain, mimicking the action of an antidepressant.[20] The antidepressant-like effects of TNFα on p11 and behaviour could be mediated by direct effects of TNFα on neurons or indirectly through neurotrophic factors,[21,22] which may be a mechanism by which TNFα produces an antidepressant-like response in rodent models of depression. IFNγ increases neurite outgrowth,[23] promotes neuronal differentiation,[24] and enhances neurogenesis,[25] which represent antidepressant-like activity.[26] These effects were inhibited by anti-inflammatory agents – ibuprofen, naproxen, acetaminophen and aspirin and the anti-inflammatory drugs antagonized both biochemical and behavioural responses to SSRIs. But, the observers had not used any selective COX-2 inhibitors in their study. Our observations of decrease in antidepressant effect of fluoxetine on co-administration of the selective COX-2 inhibitor celecoxib can be explained by the same mechanism. In the same study, the antagonistic effect of anti-inflammatory agents on antidepressant-induced behaviours was confirmed by analysis of a dataset from a large-scale real-world human study, “sequenced treatment alternatives to relieve depression” (STAR*D), underscoring the clinical significance of the findings from animal studies. However, the authors declared that it would be more appropriate to evaluate the effects of NSAIDs and other analgesics on SSRI antidepressant response in a prospective, double-blind, randomized controlled clinical study before stating a clinically significant drug interaction between NSAIDs and SSRIs.[6]

On the other hand, some researchers have suggested that TNFα and IFNγ mediate depression-behaviours caused by immune activation.[27] It was also observed that adjunctive treatment with celecoxib enhances the efficacy of both reboxetine, an SNRI, as well as fluoxetine, an SSRI in treatment-resistant depression by a different mechanism. Akhondzadeh, *et al* observed that celecoxib was effective as an adjuvant agent in the treatment of major depression in a six-week double blind and placebo controlled trial.[8] To examine the neurobiological basis of the clinical observations, Johansson, *et al* studied the acute effects of a combined treatment with celecoxib and reboxetine on noradrenaline and dopamine

output, as well as celecoxib and fluoxetine on 5-HT output in the medial prefrontal cortex, using in vivo microdialysis in awake freely moving rats. They found that celecoxib significantly potentiated the effects of reboxetine and fluoxetine on cortical noradrenaline and 5-HT output, respectively, but not the reboxetine-induced dopamine output. Moreover, celecoxib, when given alone, enhanced 5-HT output.[7] This would imply that celecoxib enhanced the antidepressant activity of reboxetine and fluoxetine by increasing concentration of monoamines in the brain. Our observations are inconsistent with the findings of these studies. Thus, the picture which emerges from this is not very clear. We see that non-selective NSAIDs have been observed in some studies to interfere with the action of antidepressants, whereas they have also been found to enhance their efficacy in others. Selective COX-2 inhibitor celecoxib however was seen to enhance the effect of SSRIs in some studies and also to correct the immune dysregulation, but did not re-balance neuroactive metabolites in others. In our study, we found that celecoxib decreased the antidepressant effect of fluoxetine when given concurrently over 21 days. Future studies will be necessary to determine the exact nature and mechanism by which NSAIDs interact with SSRIs.

CONCLUSION

We wanted to evaluate the effect of concurrent administration of selective COX-2 inhibitor celecoxib with SSRI antidepressant fluoxetine in behavioural despair models of depression in albino mice over a period of 21 days. We found that celecoxib highly significantly (P<0.000) decreased the antidepressant activity of fluoxetine when concurrently administered. This was possibly due to increase in TNFα and IFNγ and p11 protein expression in the forebrain, which enhance expression of neurotrophic factors and neurogenesis, leading to antidepressant activity. Though our results are corroborated by earlier studies, some studies have found that celecoxib enhances, rather than lowers, the antidepressant efficacy of SSRIs. Hence, there is a need for further evaluation of the nature and mechanism of drug interaction between selective COX-2 inhibitors and SSRI antidepressants over a longer duration, using diverse animal models of depression as well as clinical studies in human subjects.

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