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Role of p38 MAP Kinase Inhibitor (SB239063) and Vitamin B_{12} against Neuroinflammation

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ABSTRACT

Background: The objective of this work were to study the effect of p38 MAP Kinase inhibitor (SB239063) and Vitamin (Vit) B_{12} on activity of p38 MAP kinase implicated in neuroinflammation. "In the central nervous system (CNS) neuroinflammatin is a common feature of age-related neurodegenerative diseases. Proinflammatory cytokines, such as IL-1β and TNFα, are produced primarily by cells of the innate immune system, namely microglia in the CNS, and are believed to contribute to the neuronal damage seen in the disease". The kinase pathways that regulate the production of IL-1β and TNFα is p38 mitogen-activated protein kinase (MAPK). Recent studies suggest that Vitamin B_{12}, in addition to its known role as a co-factor in myelin formation, has important immunomodulatory and neurotropic effects. **Materials and Methods:** Male wistar albino rats (weighing about 100-200gm) were obtained from animal house of institute divided in to eight groups each group having six animals. Neuroinflammation was induced in animals by the LPS (100µg/ml) followed by treatment with MAPK inhibitor (SB239063) alone (5mg/kg) and along with Vit B_{12} (0.5mg/kg) for 30 days. **Results:** In the present study initially behavioral models (elevated plus maze apparatus, Morris water maze apparatus) were used to evaluate the memory of neuroinflammed rats which were followed by biochemical analysis. **Conclusion:** On the basis of result obtained from present study, it is observed that p38 MAPK inhibitor (SB239063) alone and in combination with Vitamin B12 is a novel therapeutic target for neuroinflammatory diseases.

Key words: P38 MAPK, Neuroinflammation, Vitamin B_{12}, Neurodegenerative diseases, Proinflammatory cytokines.

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INTRODUCTION

"Inflammation in the Central Nervous System (CNS) is a common feature of age-related neurodegenerative diseases. Cytokines are one of the primary classes of inflammatory mediators throughout the body, including the Central Nervous System (CNS). Signaling molecules that act through specific receptors and signal transduction pathways to exert a particular biological response in a target cell are cytokines. Extensive evidence from both preclinical studies and clinical animal models has showed that overproduction of proinflammatory cytokines as a contributor to pathophysiology progression in chronic neurodegenerative disorders like Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis".[1]

There are specific class of serine/threonine kinases which respond to extracellular signals such as growth factors, mitogens, and cellular stress and mediate proliferation, differentiation, and cell survival in mammalian cells. MAPKs are of four different groups within mammalian cells: the extracellular signal-related kinases (ERKs), the c-jun Nterminal kinases (JNKs), the atypical MAPKs (ERK3, ERK5, and ERK8), and the p38 MAPKs.[2] The p38 MAPKs are known as stress-activated protein kinases as they are primarily activated through extracellular stresses and cytokines and consequently have been extensively studied in the field of inflammation. Some additional roles of p38 MAPK which are becoming of interest, including the role that the p38 MAPK signaling pathway plays in neuronal function such as synaptic plasticity and neurodegenerative disease.

Vitamin B_{12} is an important micronutrient which is required in various biological processes.[3] It act as a coenzyme in folate metabolism and nucleotide biosynthesis, which makes it crucial in the metabolism of fatty acids and some amino acids and normal nervous system function.[4] Furthermore, Vitamin B_{12} deficiency results in methionine deficiency, leading to the dyes-synthesis of both phospholipids and myelin.[5] Currently, combination therapy with Vitamin B_{12} is widely combined and used in clinical patients with nerve diseases. It has been reported that systemic administration of Vitamin B_{12} promoted the recovery process from peripheral nerve damage in experimental rats.[6] Additionally, vitamin B_{12} was recently shown to be a superoxide scavenger contributing to neuronal cells axonal growth.[7] Thus, we hypothesized that Vitamin B_{12} could enhance axon formation after neuroinflammation via stabling microtubule and reducing neuronal apoptosis.

One class of p38 MAPKs inhibitor compounds, the pyridinyl imidazole's (originally named CSAIDs for cytokine-suppressive anti-inflammatory drugs), have well characterized therapeutic utility related to their inhibition of TNFa and interleukin-1beta production.[8,9] This can reduce inflammation, including the expression of other inflammatory mediators/proteins, thus significantly affecting the ultimate degree of tissue injury. CSAIDs inhibit the catalytic activity of activated/phosphorylated p38 to phosphorylate MAPKAP-K2, which upon activation serves in nuclear import/export of p38 (and itself) and provides for the phosphorylation of downstream substrates (e.g., Hsp27 for MAPKAP-K2) in the cytoplasm.[10] Not only does p38 phosphorylation/activation phosphorylate transcription factors (e.g., ATF2), it can also up-regulate protein transcription and translation and stabilize mRNA.[11]

Abundant evidences exist demonstrating that neuroinflammation contributes to the pathogenesis of several neurodegenerative disorders. This is also strengthened by epidemiological and clinical studies showing a possible protective effect of MAP kinase inhibitor (SB239063) against various inflammatory diseases like rheumatoid arthritis (RA), and inflammatory bowel disease (IBD), crohn's disease (CD). It also been seen that Vit B_{12} (cyanocobalamine) act as a co-factor in myelin formation, has important immunomodulatory and neurotropic effects.

MATERIALS AND METHODS

Materials

Animals Male albino wistar rats (weighing about 100-200 g) were used for the study. The animal were housed in standard polypropylene cages and maintained under controlled room temperature (22+2°C) and relative humidity (55+5%) with 12:12 hr light and dark cycle. All the animals were provide with commercially available normal pellet diet and water. The animals were acclimatized to laboratory conditions before behavioral experiments that were carried out between 09:00 and 17:00 h. The experimental protocol was approved by the institutional animal ethics committee, the guidelines of the Committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA) Registration no. 1446/PO/a/11/CPCSEA of the Govt. of India was followed and prior permission will be granted from the Institutional Animal Ethics Committee for conducting the experimental studies.

Chemicals

All other chemicals and reagents used which were of analytical grade were products of Sigma Aldrich Ltd., Medchemexpress and are prepared in volumetric flask using glass wares with distilled water.

Methods

Behavioral methods

In this study we were using two behavioral models namely Elevated plus maze apparatus, Morris Water Maze apparatus.

Biochemical estimations

After evaluation of behavioral test, animals were fasted overnight and blood was taken from the retro orbital plexus under mild ether anesthesia, serum was separated and used for the estimation of various biochemical parameters.

Animal grouping and treatment protocol

The animals will be divided into eight groups each containing six animals and Group 1 of normal animals will receive the vehicle normal saline at a dose of 1 ml/kg, p.o., Group 2nd is diseased control group receiving LPS (100 µgm/kg, I.P.) on 1st,7th, 14th, 21st and 30th day of study. Rest all groups are test groups. Group 3 received LPS (100 µgm/kg, I.P.) on 1st, 7th, 14th, 21st and 30th day of study +MAP kinase inhibitor, SB239063 (5 mg/kg,I.V.) on 21st to 30th day of study. Group 4 received LPS (100 µgm/kg, I.P.) on 1st, 7th, 14th, 21st and 30th day of study + Vit B12 alone (0.5 mg/kg P.O.) on 21st to 30th day of study. Group 5 received Test group received LPS (100 µgm/kg, I.P.) on 1st, 7th, 14th, 21st and 30th day of study + SB239063 (2.5mg/kg, I.V.) + Vit B12 (0.5 mg/kg P.O.) on 21st to 30th day of study. Group 6 received LPS (100 µgm/kg, I.P.) on 1st, 7th, 14th, 21st and 30th day of study + SB239063 (2.5mg/kg,I.V.) + Vit B12 (0.5 mg/kg P.O.) on 21st to 30th day of study. Group 7 received LPS (100 µgm/kg, I.P.) on 1st, 7th, 14th, 21st and 30th day of study + SB239063 (2.5mg/kg,I.V.) + Vit B12 (0.5 mg/kg P.O.) on 21st to 30th day of study. Group 8 is Standard control received LPS (100 µgm/kg, I.P.) on 1st, 7th, 14th, 21st and 30th day of study + Donepazil (1 mg/kg,P.O.).

Data analysis

Data were expressed as the mean ± Standard deviation (SD) of 9 determinations. Statistical analysis was performed using one-way Analysis of Variance (ANOVA) followed by tukey multiple comparison test. Data were considered statistically significant at $p<0.05$. All these analyses were done using Graph prism pad 7.03 Software.

RESULTS

In the present study initially behavioral models (elevated plus maze apparatus, Morris water maze apparatus) were used to evaluate the memory of neuroinflammed mice which were followed by biochemical analysis.

Assessment of memory in rats by using elevated plus maze apparatus

Results of present study are summarized in the Table 1 Results of the table reveal that administration of LPS (100µg/kg, i.p.) on 1st, 7th, 14th, 21st, 30th days caused significant increase ($p<0.01$) in transfer latency in all group. Treatment of the neuroinflammed rats by compound SB239063 from 21st to 30th day of study caused marked decrease in transfer latency (51.2±2.28), (57.0±4.00), (69.0±1.58), (65.4±2.60), (55.2±2.16) as compared to the LPS treated rats (51±2.23), (58.0±2.91) (68.8±1.92) (79.0±1.58) (86.0±2.34). Adminstration of the combination of SB239063 at a dose of 4.5 mg/kg along with Vit B_{12} at a dose of 0.5 mg/kg also caused significant reduction (51.0±2.72), (53.8±2.28) as compared to LPS treated animals. Vit B_{12} given alone and combination of compound SB239063 and Vit B_{12} at a dose of 3.5mg/kg and 0.5 mg/kg also caused moderate decrease in the ($p<0.01$) in neuroinflammed rats however combination of compound SB239063B12 at a dose of 2.5 mg/kg dose not cause any significant decrease in the transfer latency in neurotonic rats. The standard drug donepezil also provided maximum protection in neuroinflammation in LPS treated rats. Results indicates that the compound SB239063 at a dose of 5 mg/kg, i.p., alone and combination of SB239063 at a dose of 4.5mg/kg, ip.,+0.5mg/kg,. po., caused maximum improvement in T.L. and memory in neuroinflammed rats.

Assessment of memory in rats by using morris water maze apparatus.

Results of present study are summarized in the Table 2 Results of the table reveal that administration of LPS (100µg/kg,i.p.) on 1st, 7th, 14th, 21st, 30th days caused significant decrease ($p<0.01$) in T.S.T.Q. in all group. Treatment of the neuroinflammed rats by compound SB239063 from 21st to 30th day of study caused marked increase in T.S.T.Q. (26.8±2.04), (31.6±2.07) as compared to the LPS treated rats (29.4±1.34), (27.2±3.03), (23.8±2.04), (22.8±1.78),(19.6±2.07). Adminstration of the combination of SB239063 at a dose of 4.5 mg/kg along with Vit B_{12} at a dose of 0.5 mg/kg also caused significant increase (24.4±1.51), (29.8±2.95) as compared to LPS treated animals. Vit B_{12} given alone and combination of compound SB239063 and Vit B_{12} at a dose of 3.5mg/kg and 0.5 mg/kg also caused moderate increase in the T.S.T.Q. in neuroinflammed rats however combination of compound SB239063B12 at a dose of 2.5 mg/kg dose not cause any significant increase in the T.S.T.Q. in neurotonic rats. The standard drug donepezil also provided maximum protection in neuroinflammation in LPS treated rats. Results indicates that the compound SB239063 at a dose of 5 mg/kg, i.p., alone and combination of SB239063 at a dose of 4.5mg/kg, ip.,+0.5mg/kg,.po., caused maximum improvement in T.S.T.Q. and memory in neuroinflammed rats.

Assessment of serum level of cholesterol

Literature from the previous studies reveals that LPS causes activation of microglial cells as well as activation of inflammatory mediators and hypercholesterolemia in the brain and leads to neuroinflammaion. Bodovitz and klein in 1996 reported that cholesterol increases the processing of APP proteins in cell culture and also enhances brain amyloid-β accumulation. Increase level of cholesterol will increase the formation of lipid mediators of inflammation.

Results shown in the Table 3 and Figure 1 indicates that administration of LPS on 1st, 7th, 14th, and 21st day of study leads to significant increase (117.4±0.95mg/dl) in cholesterol level as compared to normal mice (85.21±1.55mg/dl). Administration of SB239063 at a dose level of 5.0mg/kg from 21st to 30 days of study caused significant decrease (88.76±1.63mg/dl) in the cholesterol level. At the dose level of 2.5mg/kg SB239063 in combination with Vit B_{12} also produce significant decrease (89.74±1.33mg/dl) in the cholesterol level but SB239063 alone produce better effect than in combination. The standard drug donepezil however has only mild effect on the cholesterol level in LPS treated mice.

As we know that p38 pathways are activated by stress and inflammation. In neuroinflammation, the formation of inflammatory mediators and cytokines causes activation of p38 MAP Kinase and leads to cell stress and death. In the present study it was found that SB239063 at higher dose level is causing decrease in brain cholesterol level, which suggests that p38MAP Kinase inhibitor also reduces cholesterol synthesis in the brain and thereby decrease neuroinflammation.

Assessment of serum level of HDL

Results in the Table 3 and Figure 2 Indicated that on administeration of LPS for 1st, 7th, 14th, 21st day of study caused significant decrease (24.14±1.58 mg/dl) in the level of HDL in neuroinflammed mice as compared to normal rats (51.13±2.94mg/dl). The reason why inflammation cause decrease in HDL level is still unclear.

Administration of SB239063 at a dose of 5.0 mg/kg caused marked increase (48.55±3.09 mg/dl) in the level of serum HDL in LPS treated rats. The standard drug donepezil (5mg/kg) also caused significant increase (32.86±2.18mg/dl) in serum HDL level in neuroinflammed rats. Result of the study suggests that SB239063 have potential to increase the HDL level in the neurotoxic rats. Restoration of the value of HDL to normal level indicates protective effect of the treatment in neurotoxicity. At lower dose level of SB239063 of 2.5mg/kg in combination with Vit B_{12} caused more significant increase (50.13±3.95 mg/dl) in HDL level in neuroinflammed rats as compare to SB239063 alone.

HDL modulates inflammation and promotes reverse cholesterol transport. HDL cholesterol severely decreases in neuroinflammation. Oxidative stress and excess levels of active oxygen species disrupt the

Table 1: Assessment of memory in rats by using elevated plus maze apparatus.

Treatment	Transfer latency on day 1 (Sec.)	Transfer latency on day 7(Sec.)	Transfer latency on day 14 (Sec.)	Transfer latency on day 21 (Sec.)	Transfer latency on day 30th (Sec.)
Group 1	49.8±1.78	50.8±1.92	50.8±1.92	50.8±1.92	50.8±1.92
Group 2	51±2.23	58.0±2.91**	68.8±1.92**	79.0±1.58**	86.0±2.34**
Group 3	51.2±2.28	57.0±4.00**	69.0±1.58**	65.4±2.60**	55.2±2.16**
Group 4	51.8±2.27	58.0±2.91**	69.4±1.67**	67.8±2.16*	63±1.87**
Group 5	51.0±2.72	57.8±3.27**	68.4±4.97**	62.4±2.30*	58.8±2.28**
Group 6	50.6±1.67	58.6±3.20**	68.2±4.91**	66.8.±1.48**	60.6±2.30**
Group 7	50.4±1.81	54.8±5.35**	68.0±2.91**	77.4±2.30**	69.4±1.94**
Group 8	50.6±1.49	55.0±5.56**	70.0±1.87**	63.6±1.67**	50.2±2.58**

The statistical significance of difference between means was calculated using one-way Analysis of Variance (ANOVA) followed by tukey multiple comparison test *$n = 6$

Values were expressed as Mean ± SEM *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ as compared to control group

Table 2: Assessment of memory in rats by using morris water maze apparatus.

Treatment	Time spent in target quartent (T.S.T.Q.) on day 1 (Sec.)	Time spent in target quartent (T.S.T.Q.) on day 7 (Sec.)	Time spent in target quartent (T.S.T.Q.) on day 14 (Sec.)	Time spent in target quartent (T.S.T.Q.) on day 21 (Sec.)	Time spent in target quartent (T.S.T.Q.) on day 30th (Sec.)
Group 1	28.8±1.64	30.2±2.28	29.0±1.00	28.8±1.78	30.6±1.81
Group 2	29.4±1.34	27.2±3.03	23.8±2.04*	22.8±1.78*	19.6±2.07**
Group 3	28.8±1.30	28.6±2.40	24.2±1.64*	26.8±2.04*	31.6±2.07**
Group 4	29.0±1.00	28.4±2.70	23.8±1.92*	24.4±1.51*	26.6±2.07*
Group 5	28.6±1.34	27.8±2.04	23.2±2.38*	26.2±1.02*	29.8±2.95*
Group 6	29.4±0.89	27.8±2.58	23.4±1.67	26.0±1.87	25.4±2.19*
Group 7	29.8±1.09	28.2±2.16	24.2±2.38*	24.2±2.28*	24.8±2.49*
Group 8	28.2±1.30	28.2±2.16	24.6±1.81	28.0±2.34*	33.8±2.04**

The statistical significance of difference between means was calculated using one-way Analysis of Variance (ANOVA) followed by tukey multiple comparison test *$n = 6$

Values were expressed as Mean ± SEM *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ as compared to control group

Table 3: Assessment of serum level of cholesterol, total lipid, HDL.

Treatment	Cholestrol (Mg/dl)	HDL (Mg/dl)	Total Lipid (Mg/dl)
Group 1	85.21±1.55	51.13±2.94	0.284±0.005
Group 2	117.4±0.9**	24.14±1.58**	0.31±0.005**
Group 3	88.7±1.63**	48.55±3.098*	0.28±0.002**
Group 4	107.1±2.04	34.81±2.51	0.299±0.004*
Group 5	89.74±1.33*	50.13±3.95**	0.285±0.04**
Group 6	94.26±2.58*	46.07±2.38*	0.294±0.003*
Group 7	106±2.77	38.26±1.87*	0.290±0.013*
Group 8	109.1±2.7**	32.86±2.18	0.298±0.03**

The statistical significance of difference between means was calculated using one-way Analysis of Variance (ANOVA) fallowed by tukey multiple comparison test *$n = 6$

Values were expressed as Mean ± SEM *P< 0.05, **P< 0.01, ***P< 0.001 as compared to control group.

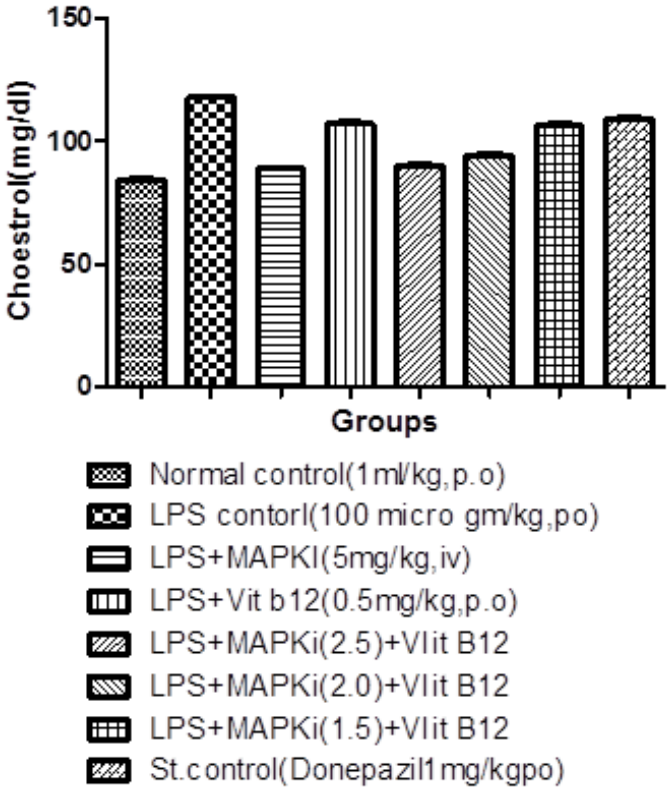

Figure 1: Effect of SB239063 on the blood serum level of cholesterol in LPS induced neuroinflammation in rats.

level of HDL in neuroinflammation. HDL is a good lipid and participates in blood cholesterol transport in the brain.

Assessment of the serum level of total lipid

Results shown in the Table 3 and Figure 3 indicates that administration of LPS on 1st, 7th, 14th, and 21st day of study leads to significant increase (0.315±0.005 gm/dl) in total lipid level as compared to normal rat (0.284±0.005 g/dl). Administration of SB239063 at a dose level of 5.0mg/kg from 21st to 30 days of study caused significant decrease (0.282±0.002g/dl) in the total lipid level. At the dose level of 4.5mg/kg SB239063 in combination with Vit B_{12} also produce significant decrease

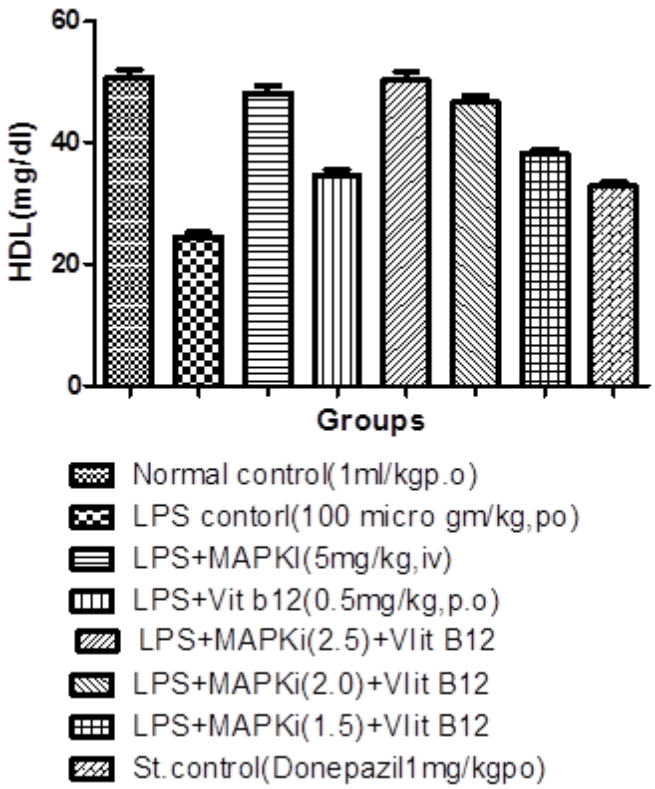

Figure 2: Effect of SB239063 on the blood serum level of total HDL in LPS induced neuroinflammation in rats.

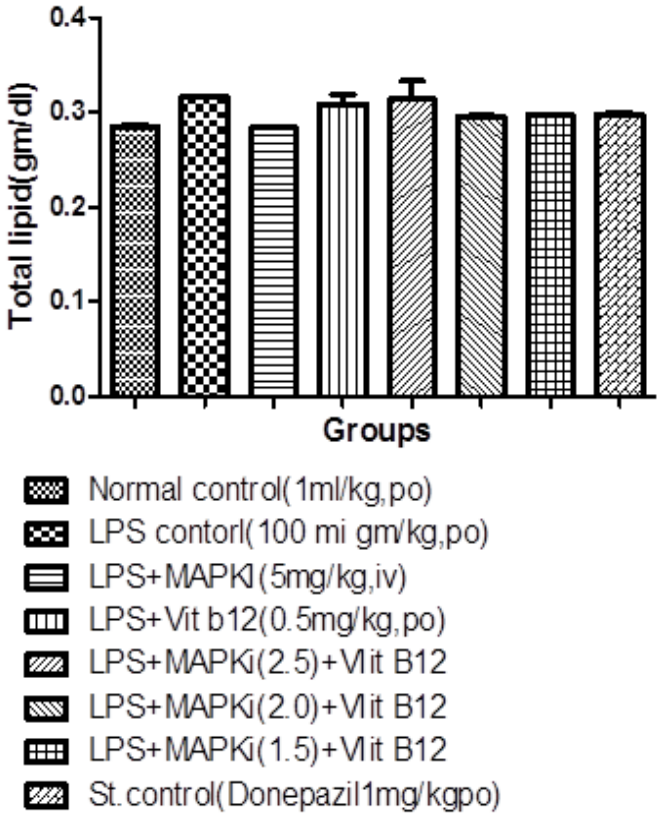

Figure 3: Effect of SB239063 on the blood serum level of total lipid in LPS induced neuroinflammation in rats.

(0.285±0.004 g/dl) in the total lipid level but SB239063 alone produce better effect than in combination. The standard drug donepezil however has only mild effect on the total lipid level in LPS treated rats.

DISCUSSION

"A significant amount of evidence suggests that the p38 MAPK (mitogen activated protein kinase) signaling cascade play a crucial role in neurodegenerative diseases. The MAPKs are a specific class of serine/threonine kinases that respond to extracellular signals such as growth factors, mitogens and cellular stress and mediate proliferation, differentiation and cell survival in mammalian cells. There are distinct groups of MAPKs within mammalian cells including p38 MAPK, ERKs and JNKs".[12] In the CNS, activation of the p38 MAPK pathway constitutes a key step in the development of neuroinflammation. Inflammatory stimuli bind to receptors of the cell surface triggering intracellular signal transduction pathways such as the nuclear factor (NFkB) pathway and the MAPK pathways.[13,14]

"Intracellular p38 MAP kinase gets activated and profoundly modulates somatic inflammatory responses. MAPK p38 signaling controls the expression of adhesion molecules, cytokines and chemokines, and a variety of other factors that mediate and control the inflammatory process. There is abounding evidence that neuroinflammation plays a major role in the pathogenesis of neurodegenration. Key cellular signaling events such as subsequent activation of mitogen activated protein kinase (MAPK) regulate neuroinflammation, neuronal survival and synaptic activity".[15]

"Irregularities in p38 MAPK signaling in neuronal cells have been associated with diseases linked with neuroinflammatory processes where persistent inflammatory stimuli such as chronic microglial activation have a damaging rather than a protective effect.[16] Prolonged and sustained activation of glial cells can result in an exaggerated inflammatory response that causes neuronal cell death through the elevated release of proinflammatory cytokines, which have a potential neurotoxic effect leading to neurodegeneration."[17,18]

This work outlines the rationale for developing therapeutics strategies against MAPK signaling network, identifying them as a novel therapeutic target for limiting neuroinflammtion. Moreover, resent studies suggest that cyanocobalamine act as a co-factor in myelin formation and has important immunomodulatory and neurotropic effect. Our result demonstrates that administration of LPS induced neuroinflammation leads to memory impairment and variation of various biochemical parameters.

These finding replicates the result of previous studies that demonstrate that activation of immune system by LPS as well as other immune challenges induced anxiogenic, reduction in locomotor activity and social activity. In our present study we have demonstrate the inhibition of p38 mitogen activated protein kinase (MAPK) pathway in animals by their suppressed locomotion and anxiogenic activity which produced required effects.

CONCLUSION

Our study suggests that P38 MAPK inhibiter (SB239063) and cyanocobalamine attenuated neuroinflammation induced by intraperitoniel endotoxin instillation in rats.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

LPS: lipopolysaccharide; **TNF:** tumor necrotic factor; **CNS:** central nervous system; **AD:** Alzheimer's disease; **PD:** Parkinson's disease; **MAPK:** Mitogen activated protein kinase; **CSAID:** cytokine-suppressive anti-inflammatory drugs; **RA:** Rheumatoid arthritis; **IBD:** inflammatory bowel disease; **CD:** crohn's disease.

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