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Original Article

Vitamin B6 Antidepressant Effects Are Comparable to Common Antidepressant Drugs in Bacillus-Calmette-Guerin Induced Depression Model in Mice

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Abstract

Objective: Bacillus-Calmette-Guerin (BCG) inoculation in mice produces an acute period of illness followed by a chronic depressive-like behavior period that lasts for few weeks. The aim was to evaluate vitamin B6 antidepressant effect in comparison with common antidepressants.
Method: BCG (0.2 ml/mouse) single dose was intraperitoneally inoculated in male mice. Vitamin B6 (100 mg/kg), fluoxetine, imipramine, or venlafaxine (10 mg/kg each) were intraperitoneally injected for 14 consecutive days following BCG administration. Illness was evaluated following inoculation and depressive-like behaviors were assessed on days 7 and 14.
Results: Illness was induced by BCG since mice lost weight and locomotor activity was reduced. Illness was prevented by vitamin B6 similar to antidepressant drugs. Despair was measured by immobility time during the forced swim test and BCG increased it compared to control (193 ± 3s vs 151 ± 7s, $P < 0.01$) on day 7, and (200 ± 5s vs 147 ± 6s, $P < 0.001$) on day 14. Vitamin B6, like antidepressants, reduced despair. BCG clearly induced anhedonia evaluated by sucrose preference test (47.5%), and it was soothed by B6 and the antidepressants. Novelty-suppressed feeding test evaluated long term depressive behavior after 14 days. BCG increased the latency to first feeding (222 ± 41s vs control 87 ± 2.6s, $P < 0.001$) and reduced food consumption per body weight (13 ± 1 mg/g vs control 19 ± 2 mg/g, $P < 0.001$) while B6 like antidepressants reduced latency and improved food consumption.
Conclusion: Vitamin B6 efficiently prevented BCG sickness and depression that was comparable to common antidepressant drugs. Therefore, B6 supplement for preventing depression in high-risk individuals is suggested for further clinical research.

Key words: *Antidepressive Agents; Anhedonia; Animal Experimentation; BCG Vaccine; Depression; Vitamin B6*

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Depression is one of the chronic disabling psychological problems leading to highly morbid complications around the globe (1). In addition to the monoamine hypothesis of depression, cytokines are another leading cause of depression (2). Continuing exposure to stress is also another pathophysiology of depression which demands prolonged antidepressant treatment (3).

The antituberculosis vaccine, Bacillus-Calmette-Guerin or BCG is weakened living Mycobacterium bovis. It is commonly used for immunization against tuberculosis in neonates. In addition to prescribing it against other Mycobacterium infections, Leprosy and Buruli ulcer, BCG is used for management of bladder cancer (4). BCG stimulates the immune system and increases indoleamine 2, 3-dioxygenase (IDO) enzyme activity in the tryptophan metabolism pathway. IDO promote tryptophan metabolism in the kynurenine pathway that results in a decrease in serotonin (5-HT) synthesis, which leads to depression (5). Studies have also demonstrated that ibuprofen, a non-steroid anti-inflammatory drug, prevented the depressive-like behavior in mice, suggesting that increase in prostaglandin and nitric oxide levels following BCG inoculation can also cause depression (6). Following inoculated mice with BCG, first, an acute period of illness appears that lasts for five days, then a chronic depressive-like behavior period results that may last for few weeks, with symptoms such as weight loss, desperate behavior, and anhedonia (7).

Evidently, nutrients have great impact on psychological health, brain function, mood, and stress response. For instance, B vitamins are important in the synthesis of neurotransmitters, thus, vitamin B1, B2, B3, B5, B6 and folate insufficiency can lead to depression (8). Vitamin B6 is freely soluble in water, it is metabolized rapidly and eliminates in the urine, especially 4-pyridoxic acid. The vitamin B6 family includes pyridoxine, pyridoxal, and pyridoxamine and their phosphorylated forms are important in regulation of neuropsychological function (9). Vitamin B6 is a cofactor of several enzymes including aromatic L-amino acid decarboxylase, which is important in the synthesis of neurotransmitters by converting 5-hydroxytryptophan to 5-HT, or L-DOPA to dopamine (10). Therefore, B6 deficiency may be involved in psychopathology of seizures, migraines, and depression (9, 11). In addition, administering vitamin B6, B12 and folate has been effective in curing depression in older people (12). According to animal studies, adding vitamin B6 to common antidepressants from different groups improved their antidepressant-like effect tested by the forced swim test and improved animal performance in the marble burring test, which evaluates repetitive and anxiety-like behavior (13).

The global estimated prevalence of depression from 2017 ranges between 2-6%, and it is seven times higher in the general population during the COVID-19 outbreak (14). COVID-19 pandemic has been a leading cause of declining psychological health due to stressful conditions, financial damages, and declining sociability (15, 16). Based on the monoamine hypothesis of depression, different types of antidepressant drugs are used in the clinic such as monoamine oxidase inhibitors, tricyclic antidepressants (TCA), tetracyclic antidepressants, serotonin selective reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs). The most important problem with these medications are the side effects such as sexual dysfunction and coronary heart disease (17). Depression prophylaxis with common antidepressant medications may unnecessarily expose vulnerable individuals to polypharmacy. Therefore, there is urgent need to introduce safe strategies to prevent depression in stressful conditions. Previous animal studies had only proven B6 antidepressant effect by acute animal models (13, 18). BCG creates a pattern of depression in animals highly resembling the pattern in humans that can be a useful model for screening possible antidepressant compounds. In this study, we investigated the effect of B6 on depression initiated by BCG vaccine and compared its efficacy with different antidepressants; imipramine (Imi; TCA), fluoxetine (Flx; SSRI), and venlafaxine (Ven; SNRI).

Materials and Methods

Animals

Male NMRI mice (6-8 weeks old, 25 ± 3 g) were used in this study. They were housed in groups of six with ad libitum access to standard mouse pellets and water. The animal cages were retained at 21 ± 2 ºC room temperature, on a 12 h bright (started at 6 AM) and 12 h dark cycle. The experiments were performed in the pharmacology behavioral laboratory from morning to early afternoon and animals were located in the laboratory 24 h before BCG inoculation. All animal experiments were conducted according to the guide for care and use of laboratory animals in science in Iran (Ethics No: IR.MUI.REC.1399.099). Best efforts were made to reduce animal suffering and to experiment using the least number of animals. Experiments were performed according to protocol in Table 1.

Drug administration

BCG vaccine (2 mg freeze-dried Mycobacterium bovis BCG/vial with 2 ml diluent (Sauton), viable particle count: 1.5-6 × 106/ml, Pasteur institute of Iran) 0.2 ml/mouse was IP inoculated (6). Pyridoxine HCl (vitamin B6 200 mg/ml, Caspian Tamin Industry, Iran) 100 mg/kg, imipramine, venlafaxine, fluoxetine (Sigma-Aldrich, India) 10 mg/kg, all were freshly prepared in normal saline and IP injected for 14 consecutive days following BCG inoculation (13, 19). The volume of injection to each mouse was 10 ml/kg body weight.

Locomotor activity test

This test was performed on days 1, 2, 3, and 7 after BCG inoculation. It was evaluated in an open apparatus and

red beams across the ground divided it into 15 zones (Borj Sanat, Iran). Each mouse was placed in the corner of the apparatus and allowed to explore for three min. Summation of number of zone entries (by moving across the red beams, the device counted horizontal activity automatically) and number standing on hind-legs (recorded by the experimenter, vertical activity) is presented as total activity count.

Forced swim test (FST)

After BCG inoculation, FST was examined on days 7 and 14. Mice were placed in a 2-liter glass beaker filled with water (25 ºC) for six min, and the first two min. were considered for habituation. The immobility time, that evaluates animal despair behavior and other activities, were measured in the last four min. The immobility time was considered when animals stay still with only minor movement to remain their head over water. Horizontal movement with four paws was measured as the swimming time; and upward activity along the tank wall was measured as the climbing time (20). In order to avoid hypothermia after the experiment, the mice were dried and placed in their cage.

Sucrose preference test

The test started from day 11 and continued for three days, two days for habituation and the test was conducted on the last day. On day one, animals had access to two similar bottles containing sucrose solution (2.5 %). On day two, one bottle was substituted with a bottle of water. On day three, exact amounts of water or sucrose solution were in the bottles and the amounts consumed were measured after 24 h (on day 14). According to the sucrose solution or water consumption, the percentage for sucrose preference (SP) was calculated. This test evaluated anhedonia that is also a depression indicator.

Novelty-suppressed feeding test (NSFT)

The test was performed in a Plexiglass box (45 × 45 × 20 cm) that was covered with 0.5 cm of wooden bedding. Three pieces of mouse chow were weighed and placed in the center of the apparatus on a Petri dish. Mice were deprived from food on day 14 after FST was completed, with no change in water supply and after 18 hours, the test started (day15). Each mouse was located in the corner of the box, the latency to feed with pellet was recorded, and finally after 30 min the total amount of food consumed was measured by weighing the remaining chow. At the end, the mice were returned to their previous cages and allowed to have access to food and water.

Statistical analysis

Data processing and statistical assessment were conducted by Excel 2016 and the GraphPad Prism 7 (La Jolla, CA, USA) software programs. Results were expressed as mean ± SEM, BCG results were compared with the control group by t-test, B6 and the antidepressants results were compared with BCG results by one-way analysis of variance (ANOVA) and completed by Tukey's multiple comparison tests, P values less than 0.05 were considered statistically significant.

Results

Weight changes

As shown in Table 2 animals that received BCG did not gain weight after a week. By administrating B6, Flx, and Imi, body weight significantly increased while Ven did not improve weight. After 14 days, BCG significantly induced weight loss in mice compared with control ($P < 0.01$), while administration of B6, or the antidepressants (Flx, Imi, and Ven), prevented weight loss and significantly increased animal weight compared with the BCG group ($P < 0.05$).

The locomotor activity test

As it is shown in Figure 1, in the control group, locomotor activity was reduced on days 3, and 7 ($P < 0.05$). In the BCG group, the locomotor activity on days 2, 3, and 7 were lower than the first day ($P < 0.05$). In B6 treated animals, no locomotor activity change was observed during 7 days. In Imi treated mice, locomotor activity on days 3 and 7 were lower than the first day, and, in Flx treated animals, it was lower on day 7 ($P < 0.05$). After the third day, the locomotor activity in different study groups became constant. There was no important difference between any of the groups with the normal animal group on different days of manipulation. While by treating the animals with Imi, locomotor activity was significantly lower than the BCG inoculated group on days 3 and 7 ($P < 0.05$).

The FST test

As shown in Figure 2, the BCG inoculation significantly augmented the immobility time during the FST; on day 7, it was 193 ± 3s ($P < 0.01$, vs control 151 ± 7s), and on day 14 it was 200 ± 5s ($P < 0.001$, vs control 147 ± 6s). Treatment with B6 significantly reduced immobility time on day 7 (140 ± 8s, $P < 0.05$) and on day 14 (117 ± 9s, $P < 0.001$) compared with the BCG group. The antidepressant drugs also significantly reduced immobility time compared with the BCG group. As it is shown in Table 3, the swimming time measured following BCG inoculation was significantly lower than control ($P < 0.001$). Treatment with B6 or the antidepressants significantly increased the swimming time compared with the BCG group. Treatment with Ven significantly increased the climbing time compared with the BCG group on days 7 and 14 ($P < 0.01$).

The SP test

The SP level lower than 65% was considered as anhedonia (21). As presented in Table 4, BCG reduced the SP that clearly indicated anhedonia, while treatment with B6 or the antidepressants improved the SP value.

The NSFT test

As presented in Figure 3A, BCG inoculation significantly increased the latency to feed in NSFT (222

± 41s) compared to the control group (87 ± 2.6s, P < 0.001). Treatment with B6, like the antidepressant drugs, significantly reduced latency compared to the BCG group (P < 0.001). In addition, BCG significantly reduced total amount of food consumption during NSFT (13 ± 1 mg/g body weight) compared with the control group (19 ± 2 mg/g body weight, P < 0.001) (Figure 3B). Treatment with B6 significantly increased food intake (17 ± 1.6 mg/g body weight) compared with the BCG group (P < 0.05). Treatment with Flx, Imi, and Ven also improved food intake in animals.

Table 1. Research Protocol Timeline, Indicating the Timing of BCG Inoculation, B6, Antidepressant Drugs Administration, and the Behavioral Tests Performed in Mice

Days	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
BCG	✓															
B6, Flx, Imi, Ven		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Locomotor activity test		✓	✓	✓				✓								
FST								✓							✓	
SP test												H	H	✓	✓	
NSFT															F	✓

✓: Treatment or experiment performed, -: no treatment or experiment, H: habituation, F: fasting, FST = Forced swim test, SP: sucrose preference, NSFT: Novelty-suppressed feeding test, Imi: imipramine, Flx: fluoxetine, Ven: venlafaxine. Fasting was imposed after FST was completed on day 14.

Table 2. Effect of BCG Inoculation, B6 and the Antidepressant Drugs on Percentage of Body Weight Change after 7 and 14 Days

Groups (n = 6)	Control	BCG	BCG + B6	BCG + Flx	BCG + Imi	BCG + Ven
7 Days weight change (%)	5.2 ± 1.7	0.3 ± 2.8	7.3 ± 1.5	8.2 ± 0.8*	3.5 ± 3.17	-0.1 ± 0.7
14 Days weight change (%)	11 ± 2.8	-4 ± 2.7^^	5.9 ± 1.7*	9.4 ± 3.5*	6.3 ± 3.3*	4.4 ± 2*

The results present mean ± SEM, BCG was compared with the control group by t-test, B6 and the antidepressants were compared with BCG by ANOVA, and Tukey's multiple comparison tests. ^^ P < 0.01 compared with the control group, * P < 0.05 compared with BCG group. Imi = imipramine, Flx = fluoxetine, Ven = venlafaxine.

Table 3. Effect of BCG Inoculation, B6 and the Antidepressant Drugs on Swimming and Climbing Time Behavior in Forced Swim Test after 7 and 14 Days

Groups (n = 6)	Swimming Time (s)		Climbing Time (s)	
	Day 7	Day 14	Day 7	Day 14
Control	69 ± 4	72 ± 5	16 ± 4	32 ± 6
BCG	33.6 ± 3#	30 ± 4#	13 ± 4.5	9 ± 2.5
BCG + B6	87 ± 6*	97 ± 13***	16 ± 3	22 ± 5
BCG + Flx	77 ± 15*	140 ± 4***,#	28 ± 8	9.5 ± 3
BCG + Imi	90 ± 16*	136 ± 7***,#	21 ± 8	24 ± 11
BCG + Ven	132 ± 9***,^	133 ± 14***,#	52 ± 11**,^	66 ± 14**

The results present mean ± SEM, BCG was compared with the control group by t-test, B6 and the antidepressants were compared with BCG and evaluated by ANOVA, followed by Tukey's multiple comparison tests. ^ P < 0.05, # P < 0.001 were compared with the control group, * P < 0.05, ** P < 0.01, *** P < 0.001 were compared with the BCG group. Imi = imipramine, Flx = fluoxetine, Ven = venlafaxine.

Table 4. Sucrose Preference Percentage Following BCG, B6 and Antidepressant Drug Administration

Groups	Control	BCG	BCG + B6	BCG + Flx	BCG + Imi	BCG + Ven
% SP	74	47.5	65.6	81	72	77.5

Sucrose preference percentage = (sucrose intake/sucrose plus water intake) × 100. Imi = imipramine, Flx = fluoxetine, Ven = venlafaxine.

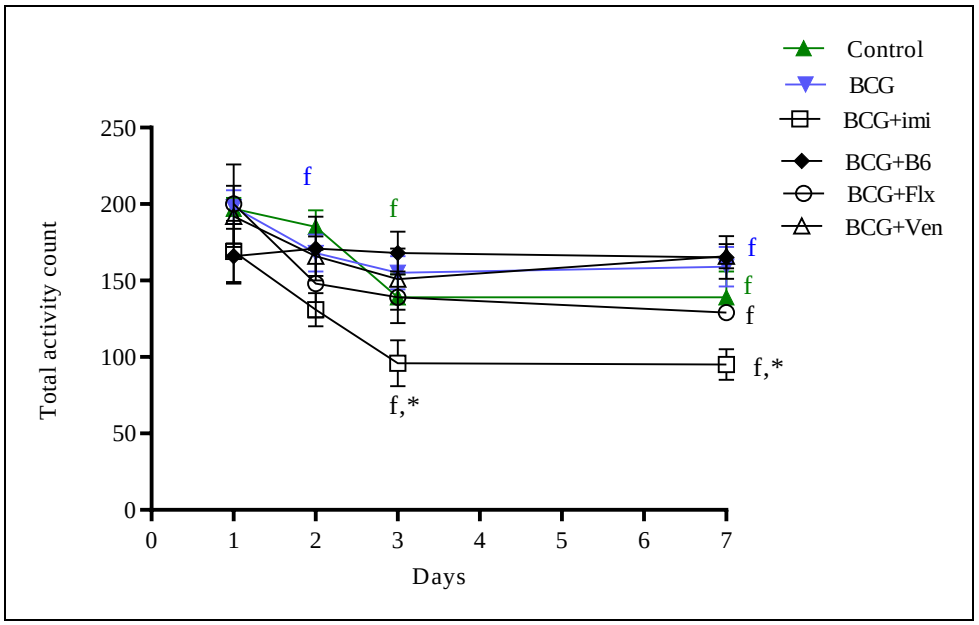

Figure 1. Effect of BCG, B6, and the Antidepressant Drugs on the Locomotor Test

Total activity count equals the sum of horizontal and vertical movements. The results present mean ± SEM and were evaluated by ANOVA and Tukey's multiple comparison tests. For each of the treatments during the 7 days, f had P < 0.05 compared with locomotor activity on the first day * P < 0.05 was compared with the BCG group. Imi = imipramine, Flx = fluoxetine, Ven = venlafaxine.

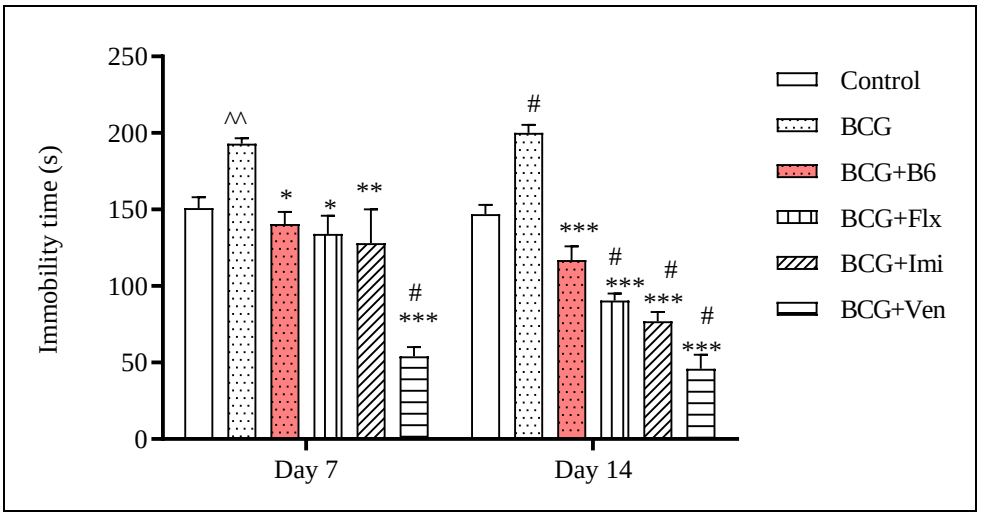

Figure 2. Effect of BCG Inoculation, B6 and the Antidepressant Drugs on the Immobility Time during Forced Swim Test after 7 and 14 Days

The results present mean ± SEM. BCG was compared with the control group by t-test. B6 and the antidepressants were compared with BCG and evaluated by ANOVA and Tukey's multiple comparison tests. ^^ P < 0.01, # P < 0.001 were compared with the control group. * P < 0.05, ** P < 0.01, *** P < 0.001 were compared with the BCG group. Imi = imipramine, Flx = fluoxetine, Ven = venlafaxine.

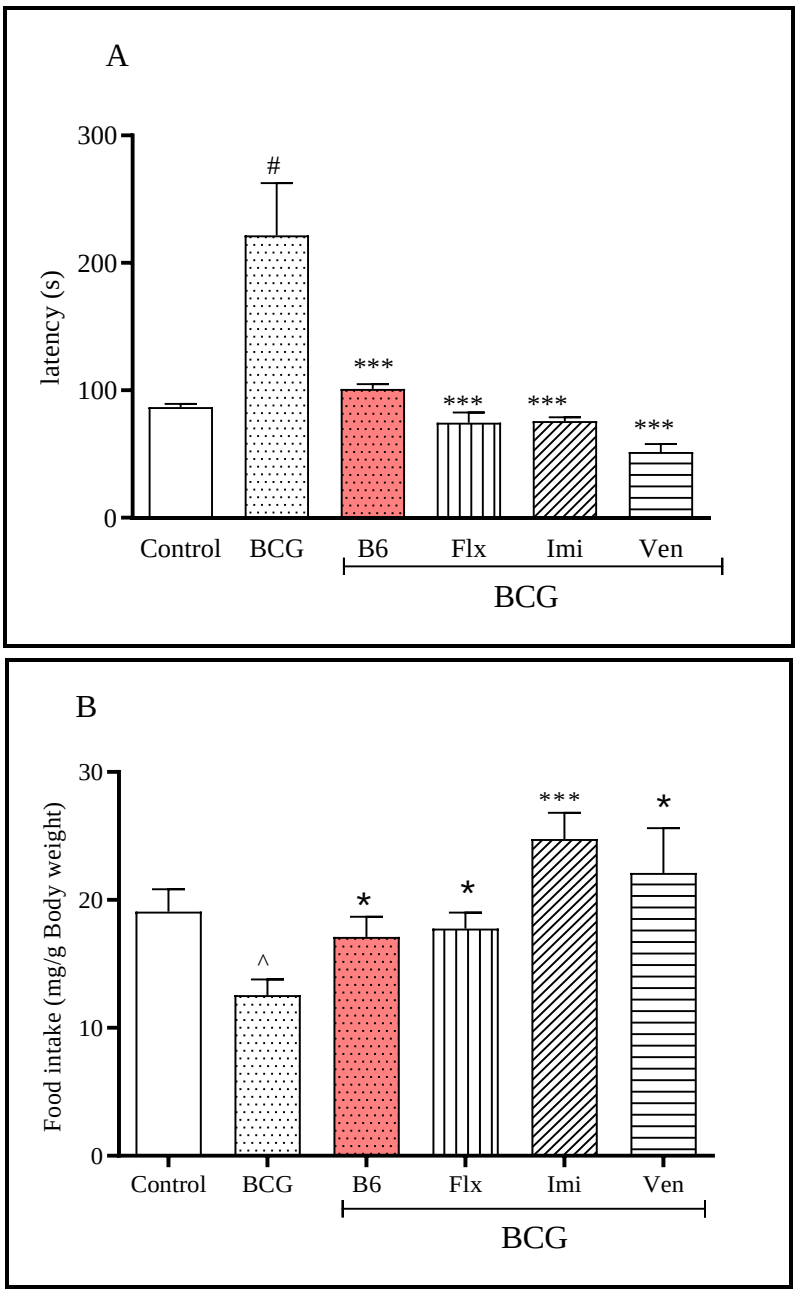

Figure 3. Effect of BCG Inoculation, B6 and the Antidepressant Drugs on Latency (A) and Food Intake (B) During the Novelty-Suppressed Feeding Test after 14 Days

The results present mean ± SEM. BCG was compared with the control group by t-test, B6 and the antidepressants were compared with the BCG group and analyzed by ANOVA and Tukey's multiple comparison tests. ^ $P < 0.05$, # $P < 0.001$ were compared with the control group, * $P < 0.05$, *** $P < 0.001$ were compared with the BCG group. Imi = imipramine, Flx = fluoxetine, Ven = venlafaxine.

Discussion

These findings proved that vitamin B6 prevented BCG induced depression in mice that was comparable to the antidepressant drugs (Flx, Imi, and Ven). The antidepressant effects were evaluated by different acute and chronic models: as immobility time decreased during FST, SP increased, and latency to feed decreased and food consumption increased during NSFT.

The antidepressant effects of B6 were previously reported in acute models of animal depression. These models have strong predictive validity but lack face validity because depression in humans is a chronic illness (13, 18). Advantages of depression induced by BCG include simplicity of application, low cost, and its resemblance to MDD in humans as a chronic ailment. BCG causes various alterations in brain neurochemistry,

neuronal immune and endocrine function, and behavioral changes that all correspond with MDD (7).

In order to understand BCG induced sickness in mice, weight and locomotor activity were evaluated (22). Animals were not able to gain weight after a week of BCG injection and after two weeks, their weights decreased (Table 2). Inflammation and cytokines are associated with the sickness behavior (7). Plasma levels of interleukin-1β (IL-1β), a key cytokine in development of initial sickness behavior increases (23). Additionally, BCG induces a boost of Interferon-γ, tumor necrosis factor-α, and IL-6 concentrations (7). Previously, the sickness induced by BCG was shown to reduce weight, however, in experiments, a maximum weight reduction was observed after 2 days that was recovered after 12 days (24). Another study has shown a significant body weight difference from control group for seven days (7). These studies used different BCG inoculation methods, and, same as our experiments, they have observed serum sickness effects.

Locomotor activity significantly reduced 1 day after BCG inoculation and became stabilized after 2days. Indicating sickness behavior that was in agreement with previous results (24). After a week, there was no noticeable difference between locomotor activities of the experimental groups (except the Imi group) from the control animals. This was in agreement with previous results that showed no difference in the locomotor activity after 14 days of BCG inoculation (6). By administering B6, locomotor activity remained constant during the experiment. Ven and Flx only slightly reduced the immobility time. Therefore, B6 similar to Flx and Ven antidepressants prevented sickness by BCG administration since they not only prevented weight reduction but also improved locomotor activity. While by administering Imi, locomotor activity dropped to the lowest level after three days and remained low after a week. Since Imi also improved animals' weight, it was assumed that sickness was prevented and this different effect observed with Imi may be the direct effect of Imi itself that was also observed previously (25), or it could be due to interaction of Imi and BCG serum sickness effect.

The immobility time during the FST sharply increased seven days after administration of BCG and remained high after 14 days, which clearly showed depressive-like effect. Therefore, after the sickness period of the first week, depressive behavior was observed and persisted over a week. BCG inoculation activated peripheral and brain IDO in mice for about three weeks followed by decrease in tryptophan levels that coincides with long-term behavioral depressive-like changes (7). Vitamin B6, like the antidepressants (Flx, Imi, and Ven), reduced immobility time. It was previously suggested that B6 antidepressant-like effects may be related to the noradrenergic system since its effect was hampered by α-methyl-p-tyrosine during FST in mice (26). Beyond that, regulation of mood is highly related to tryptophan metabolism and serotonin production. Pyridoxal phosphate is a necessary cofactor in decarboxylation reactions in tryptophan metabolism and its conversion to the monoamine neurotransmitter, serotonin, is necessary (10). During the FST, as the immobility time indicates, animal despair behavior, evaluated by swimming and climbing, indicates the possible involvement of serotonergic or catecholaminergic involvement. The SSRI drugs increase the swimming time while the catecholamine related antidepressants increase the climbing time (20). One and two weeks after BCG inoculation, the depression-like behavior was accompanied by more influence on the swimming time than climbing time; it could be assumed that the serotonergic system was mostly suppressed. Although in our observational study neurotransmitters were not evaluated, but previous results support our deduction. It was noted earlier that BCG induces IDO which shifts tryptophan metabolization to quinolinic acid, thus, decreasing serotonin production; a neurochemical change related to depression (27). B6 along with other antidepressant drugs (Flx, Imi, and Ven) increased the swimming time (Table 3). In addition, Ven also increased climbing time denoting its effect on the serotonin and norepinephrine system. Anhedonia is another feature of depression that could be evaluated by SP in animal models (28). This test showed parallel results similar to the FST results. The animals' SP increased following B6 administration or the antidepressant drugs.

One disadvantage of FST is that it lacks face validity since it measures acute depression but depression is a chronic disease. The NSFT on the other hand measures depressive behavior following chronic antidepressant administration (29). The basis of this test is hyponeophagia related to decrease in feeding produced by exposure to a new environment. Generally, by presenting mice with food in a new environment such as an unfamiliar cage, anxiety is produced and hyponeophagia is evaluated by measuring the latency to feed and the total food consumed. The point is that in experimental animal, while acute treatment with anxiolytic drugs is effective, only chronic treatment with SSRIs and TCA is effective in decreasing latency period until feeding (30, 31). BCG as a chronic model of depression clearly increased the latency to feed and the food intake was lower than normal animals in NSFT. Consequently, we showed that NSFT is an appropriate test while evaluating depressive-like behavior in the chronic BCG model of depression. Administering B6 like the antidepressant drugs (Flx, Imi, and Ven) reduced latency and increased food ingestion during NSFT that supported vitamin B6 antidepressant effects.

Limitation

In this behavioral pharmacological study, serum and brain neurotransmitters (such as 5-HT, and

catecholamines), their metabolites in the urine, and IDO activity were not evaluated.

Conclusion

These experiments revealed that B6 is efficient in preventing BCG induced sickness and depression and was comparable with various antidepressant drugs (Flx, Imi, and Ven). Administering antidepressant drugs for preventing depression in high risk individuals may unnecessarily expose them to chemicals, side effects, and polypharmacy. Therefore, further clinical studies are suggested for evaluating B6 as a harmless supplement to avoid depression in high risk individuals such as patients experiencing stressful conditions. In addition, neurological changes produced by B6 following BCG induced depression is suggested for further studies.

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Conflict of Interest

Authors certify that no conflict of interest in relation to this article exists.

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