Cognitive Enhancement Effects of *Bacopa Monnieri* (Brahmi) on Novel Object Recognition and NMDA Receptor Immunodensity in the Prefrontal Cortex and Hippocampus of Sub-Chronic Phencyclidine Rat Model of Schizophrenia

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Background: *Cognitive impairment is a common characteristic in schizophrenia that cannot be attenuated by antipsychotics. Brahmi, popularly known as a cognitive enhancer, might be a new frontier of cognitive deficit treatment in schizophrenia.*
Objective: *To study effects of Brahmi on attenuation at cognitive deficit and cerebral glutamate/N-methyl-D-aspartate (NMDA) receptor density in sub-chronic phencyclidine (PCP) rat model of schizophrenia.*
Material and Method: *Rats were administered PCP or vehicle. Half of the PCP-group was treated with Brahmi. Discrimination ratio (DR) representing cognitive ability was obtained from novel object recognition task. NMDA immunodensity was measured in prefrontal cortex, striatum, cornu ammonis fields 1 to 3 of hippocampus (CA1-3), and dentate gyrus (DG) using immunohistochemistry.*
Results: *DR in PCP-group was significantly decreased compared with control. This occurred alongside NMDA up-regulation in prefrontal cortex and CA1-3, but not in striatum and DG. PCP with Brahmi showed a significant increase in DR score compared with PCP alone. This occurred alongside significant decrease in NMDA immunodensity in prefrontal cortex and CA1-3. No significant difference in cerebral NMDA immunodensity was observed between PCP with Brahmi and control.*
Conclusion: *Cognitive deficit observed in PCP-administered rats was mediated by NMDA up-regulation in prefrontal cortex and CA1-3. Interestingly, Brahmi could recover this cognitive deficit by decreasing NMDA density in these brain areas to normal.*

Keywords: *Brahmi, Schizophrenia, Animal model, Novel object recognition, NMDA receptor*

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Schizophrenia is the most common psychotic disorder, which affects 1% population around the world. The characteristics of the disorder are positive symptoms (e.g. hallucination, delusions, thought disorder, perceptual disturbances, and increased motor function), negative symptoms (e.g. alogia, anhedonia, flat affect, avolition, and social withdrawal), and cognitive deficit. To date, treatments with antipsychotics are effective in reducing positive symptoms but not fully effective in treatments of negative symptoms and cognitive deficit. Cognitive impairment is a major problem contributing to a patient's functional disability and restriction on quality of life.

Although it seems impossible to produce schizophrenia in an animal, a few animal models have been accepted and widely utilized as models for schizophrenia. One valuable model is a sub-chronic administration of phencyclidine (PCP), which is a non-competitive glutamate/N-methyl-D-aspartate (NMDA) receptor antagonist to rats. This model came from the finding that PCP can induce psychosis, which expressed both positive and negative symptoms similar to schizophrenia[1,2]. Rats receiving sub-chronic PCP administration have shown the behavioral changes that are relevant to those found in schizophrenic patients. These behavioral changes include locomotor hyperactivity and sensorimotor gating deficits[3].

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Sub-chronic PCP administration can also produce deficits in learning and memory in rats[4,5].

An up-regulation of cortical NMDA receptor subunit 1 (NMDAR1) and NMDA receptor subunit 2 (NMDAR2) has been reported in rats receiving sub-chronic PCP administration[6]. This PCP-induced NMDA receptor up-regulation has been suggested to produce cortical apoptosis[7], which may implicate cognitive deficits in schizophrenia. NMDA receptor up-regulation has also been reported in a variety of brain regions in schizophrenic patients. Previous studies reported increases in NMDA receptor above control values in post-mortem putamen and temporal cortex of schizophrenic patients by measuring the density of radioligand binding [^{3}H] L-689,560 to the glycine site of the NMDA receptor[8], which was interpreted as receptor up-regulation in response to glutamatergic hypofunction.

Typical antipsychotic drugs have shown a great impression on reducing positive symptoms and disabilities in schizophrenia. However, they can produce severe side effects including extrapyramidal movement disorders[9]. Moreover, they are not effective at attenuating negative symptoms[10]. To date, atypical antipsychotic drugs have been defined as highly effective drug treatment in schizophrenia due to the capability of reducing the incidence of extrapyramidal symptoms and alleviating the negative symptoms. However, they are more likely to induce weight gain and obesity related diseases[11].

Cognitive impairment is a major problem that leads to functional disability in schizophrenia. It persists even after psychotic symptoms have already been attenuated. Atypical antipsychotics clozapine and risperidone have been reported to reverse PCP-induced deficits in object recognition[5]. However, they are more likely to produce such side effects as mentioned above.

There is evidence to suggest that some alternative medicines may have cognitive enhancement effect with fewer side effects. *Bacopa monnieri* or Brahmi is a traditional Indian Ayurvedic medicinal plant that has been defined as herbal therapeutics to boost memory, restore cognitive deficits, and improve mental function[12]. A recent study has reported that long-term oral administration of bacosides, the active saponins of Brahmi, can prevent age-associated neurodegeneration and promote healthy brain ageing in female Wistar rats[13]. Additionally, it has been reported that Brahmi can reduce beta-amyloid levels in the brain of transgenic mouse model of Alzheimer's disease[14]. Consistent with the previous study in humans, Brahmi extract has been reported to enhance cognitive performance in ageing[15].

The main purpose of the present study was to assess whether administration of Brahmi was able to attenuate the effect of sub-chronic PCP administration on cognition, assessed using the novel object recognition paradigm and on the density of NMDA receptor in the prefrontal cortex, striatum, and hippocampus.

Material and Method

Animals

Twenty-seven male Wistar rats weighing 200 to 220 g were obtained from the National Animal Center, Mahidol University, Thailand. The animals were housed one per cage and maintained at 21±2°C under a 12 h/12 h light/ dark cycle with food and water available ad libitum in the home cage. All animals were acclimatized for seven days before experiment. All animal procedures were performed in accordance with Mahidol University Code of Practice and the National Institutes of Health (USA) Guidelines for treatment of laboratory animals. The protocol for the present study was approved by the Animal Research Committee of Thammasat University, Thailand. The number of project license for animal experiment in the present study is AE 007/2552.

Drugs and drug administration

Animals were assigned to three groups (n = 9/group);

Control group

Animals received intraperitoneal injection (i.p.) of vehicle solution (0.9% NaCl) bi-daily (08:00 and 16:00 h) for seven days then they received orally the vehicle solution (distilled water) daily (08:00 h) for 14 days.

Sub-chronic PCP group

Animals received 2 mg/kg of PCP i.p. bi-daily (08:00 and 16:00 h) for seven days then they received orally the vehicle solution (distilled water) daily (08:00 h) for 14 days.

PCP + Brahmi group

Animals received 2 mg/kg of PCP i.p. bi-daily (08:00 and 16:00 h) for seven days then they received orally 40 mg/kg/day of Brahmi daily (08:00 h) for 14 days. PCP HCl (Sigma, USA) and Brahmi (Planetary™ Herbals) were dissolved in 0.9% NaCl and distilled water, respectively.

Novel object recognition test

Novel object recognition test was performed in all groups of animals a week after drugs or vehicle administration. The test took place in a room with 360 lux lighting. The apparatus consisted of a solid black plastic box (63 cm x 63 cm x 45 cm) that was placed on the floor throughout the experiment. A video recorder (Canon) was positioned on a movable trolley above the plastic box in order to record behavior. The objects to be discriminated were made of glass, plastic, or ceramic. During the task, the bottoms of objects were fixed by the adhesive tape in order not to be displaced by the animals. In the three days prior to the novel object recognition test, all rats were initially habituated to the empty box for three sessions of three minutes daily. In the novel object recognition test, each rat was placed in the box and exposed for three minutes to two identical objects placed approximately 10 cm apart in the center of the box. The rat was then returned to its home cage for an hour. The box and the objects were cleaned with 70% ethanol. Both objects in the box were replaced, one with an identical object and another with a novel object. Rats were then returned to the novel object recognition box and allowed to explore the objects for three minutes. All trials were recorded and behavioral analysis was carried out blind to treatment. Object exploring included rat sniffing, licking, or touching the objects. The data were expressed as the discrimination ratio (DR) calculated from the following equation; DR = [(time exploring novel object-time exploring familiar object)/total exploration time)].

NMDAR1 immunohistochemistry

After novel object recognition test was undertaken, rats were sacrificed, and whole brains were removed and fixed in 4% paraformaldehyde. All animal tissues were paraffin-embedded sections that were sectioned coronally at a thickness of 5 μm then mounted onto 3-aminopropyltriethoxysilane (APES) coated glass slides. For the sectioning, levels with respect to Bregma were determined with the use of a rat brain stereotaxic atlas[16]. The sections for prefrontal cortex were taken between Bregma 2.7 to 2.2 mm while those for striatum were taken from Bregma 0.7 mm. Sections for hippocampus were sectioned posterior to Bregma 3.3 mm. The sections were dewaxed in xylene then rehydrated in 100%, 90%, and 70% ethanol and washed for five minutes in distilled water. The sections were immersed in phosphate buffer saline (PBS; 0.01 M phosphate buffer, 0.9% NaCl, pH 7.4) and heated in a microwave oven on full power (650 W) for three periods of five minutes in order to aid antigen retrieval. The sections were left at room temperature for 30 minutes to cool down then incubated in a solution of 5% H_2O_2 in 10% methanol and 0.1% Triton X-100 in PBS pH 7.4 to inhibit endogenous peroxidase activity and then washed for three x five minutes in PBS. Non-specific binding was minimized by incubation for one hour in 5% normal goat serum in PBS, followed by incubation at 4°C overnight with a polyclonal antibody against the glutamate/NMDA receptor subunit1 (NMDAR1) (Sigma, USA) at a dilution of 1:1,000 in blocking solution. The sections were washed for three x five minutes in PBS before incubation for two hours at room temperature with biotinylated secondary antibody (anti-goat IgG) diluted 1:200 in protein blocking solution. Sections were processed by the avidin-biotin method using a Vectastain ABC kit (Vector Laboratories, UK) and peroxidase was visualized using 3',3'-diaminobenzadine (DAB) intensified with nickel chloride. The sections were dehydrated and mounted. Negative control sections were processed as for NMDAR1 immunohistochemistry except that the primary antibody was omitted. No immunostaining could be detected under these conditions. All slides were coded and analyzed blind to treatment.

Image analysis

NMDAR1 immunostained neuronal densities were measured in the prefrontal cortex and cornu ammonis fields 1-3 (CA1-3) using Image ProPlus software. CA1-3 was subdivided into CA1 and CA2/3. NMDAR1 immunoreactivity in the dentate gyrus (DG) and striatum were quantified by integrated optical density (IOD) using Scion Image Software based on NIH image (v. beta 3b; www.scioncorp.com; 1998). The value of IOD is the sum of the optical densities of all pixels in the region divided by the number of pixels and it was quantified by subtracting the background of the section. For IOD analysis, five regions of interest were measured in striatum and DG of all sections. The average of values from five regions of interest in each brain subfield of each rat was used for statistical analysis. Neuronal density and IOD were measured blind to the animal groups.

Statistical analysis

The data are expressed as mean ± SEM. One-way ANOVA was performed to determine the effect of treatment on discrimination ratio, followed

by post hoc statistical comparison of treatment group. NMDAR1 neuronal densities and IOD of each brain region were analyzed using one-way ANOVA with post hoc comparison of treatment group. Independent t-test was used to compare the discrimination ratio and NMDAR1 immunodensity between PCP and PCP with Brahmi groups. Statistical significances were defined as $p<0.05$. All statistical analysis was performed using SPSS V13 for windows (SPSS Inc., Chicago, USA).

Results

Novel object recognition test

One-way ANOVA with Dunnett post hoc tests revealed a significant reduction in discrimination ratio in sub-chronic administration of PCP ($p<0.001$) and PCP with Brahmi ($p<0.01$) compared with control. Independent t-test revealed a significant increase in DR score in PCP with Brahmi ($p<0.001$) compared with PCP alone (Fig. 1).

NMDAR1 immunohistochemistry

Immunohistochemistry demonstrated NMDAR1 immunoreactive cells in prefrontal cortex, striatum, pyramidal cells of CA1, CA2/3, and granule cells in the granular layer of the DG (Fig. 2). Neuronal density was measured in the prefrontal cortex, CA1 and CA2/3 of hippocampus whereas integrated optical density was measured in striatum and DG. One-way ANOVA with Dunnett post hoc tests revealed a significant increase in NMDAR1 neuronal density in prefrontal cortex in sub-chronic PCP administration group ($p<0.05$) compared with control. No significant difference in NMDAR1 neuronal density was observed between the PCP with Brahmi group and control in this brain region and independent t-test showed no significant difference between PCP alone and PCP with Brahmi groups (Fig. 3). Dunnett post hoc analysis showed that NMDAR1 neuronal density was significantly increased above control in sub-chronic administration of PCP in CA1 ($p<0.01$) (Fig. 4) and CA2/3 ($p<0.01$) (Fig. 5). However, no significant difference was observed in these areas between PCP with Brahmi and control. A significant decrease in NMDAR1 neuronal density was observed in PCP with Brahmi in CA1 ($p<0.01$) (Fig. 4) and CA2/3 ($p<0.05$) (Fig. 5) compared with PCP alone. No significant difference was observed in optical density in either striatum or DG (Fig. 6) compared between groups of experiment.

Discussion

The present study showed deficits in novel object recognition in animals receiving sub-chronic

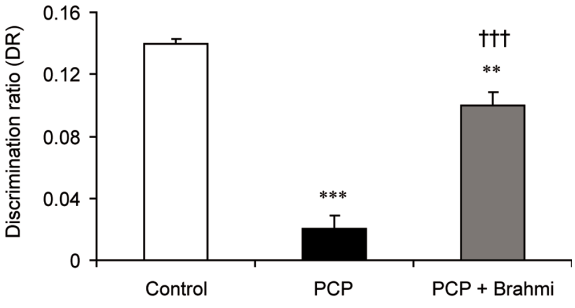

Fig. 1 Discrimination ratio in control, PCP and PCP with Brahmi groups obtained from novel object recognition task. Data are mean ± SEM.
** $p<0.01$, *** $p<0.001$ vs. control, ††† $p<0.001$ vs. PCP

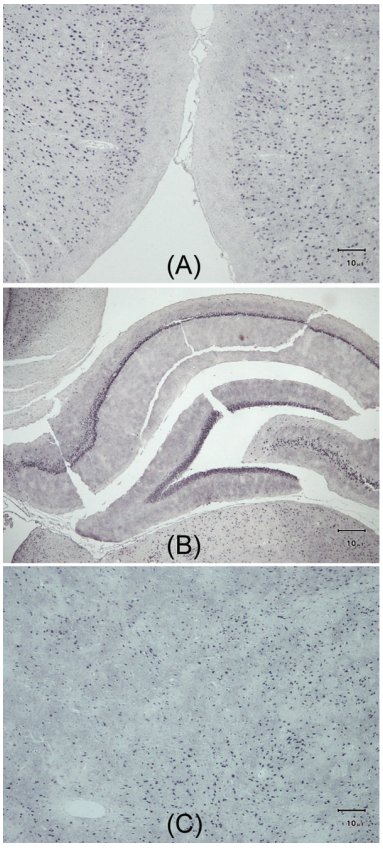

Fig. 2 Immunohistochemistry and brightfield photomicrograph of coronal sections showing the distribution of NMDAR1 immunoreactivity throughout the rat (A) prefrontal cortex, (B) hippocampus, and (C) striatum (4x magnification).

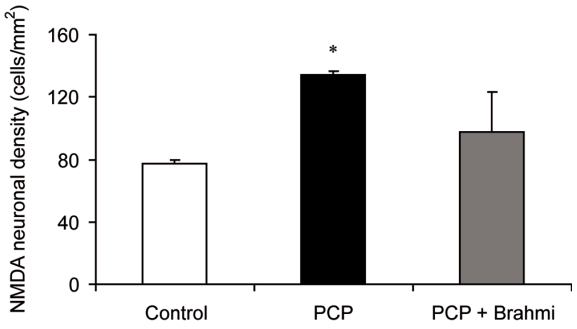

Fig. 3 NMDAR1 immunodensity in the prefrontal cortex in control, PCP and PCP with Brahmi groups. Data are mean neuronal density ± SEM. * p<0.05 vs. control

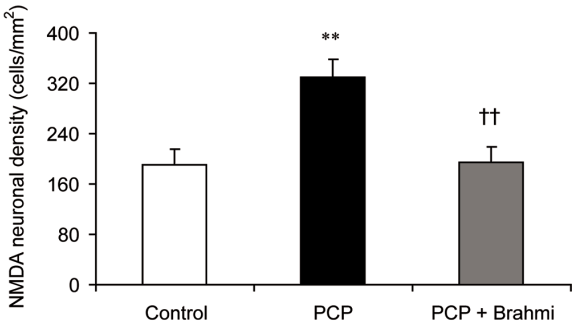

Fig. 4 NMDAR1 immunodensity in the pyramidal layer of CA1 in control, PCP and PCP with Brahmi groups. Data are mean neuronal density ± SEM. ** p<0.01 vs. control, †† p< 0.01 vs. PCP

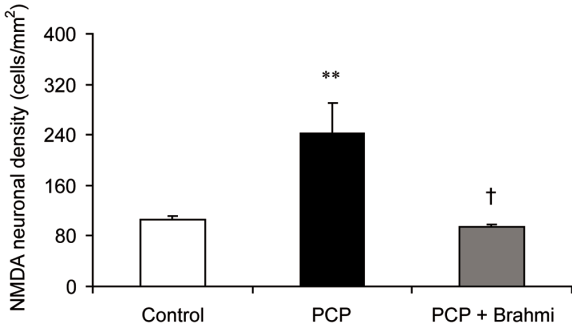

Fig. 5 NMDAR1 immunodensity in the pyramidal layer of CA2/3 in control, PCP and PCP with Brahmi groups. Data are mean neuronal density ± SEM. ** p<0.01 vs. control, † p< 0.05 vs. PCP

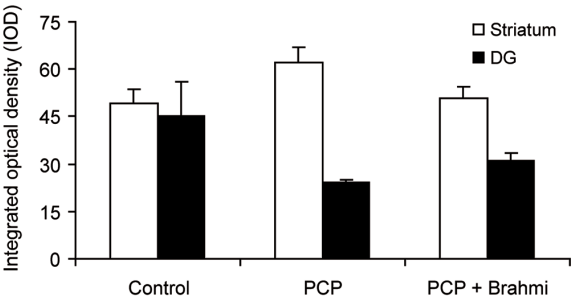

Fig. 6 NMDAR1 immunodensity in the striatum and granule layer of DG in control, PCP and PCP with Brahmi groups. Data are mean integrated optical density ± SEM.

PCP administration. The deficits in DR scores in this animal group occurred alongside increases in NMDAR1 neuronal densities in the prefrontal cortex, CA1 and CA2/3 of the hippocampus. Receiving Brahmi after sub-chronic PCP administration, animals significantly improved object recognition memory although it did not reach the normal level as in the control group. Additionally, NMDAR1 neuronal densities in this group were significantly decreased to normal level. These results interpreted that cognitive deficits occurred in the sub-chronic PCP administration rat model of schizophrenia. However, it could be recovery after Brahmi administration. Additionally, this cognitive enhancement effect of Brahmi might be due to down-regulation of NMDAR1 receptor in the prefrontal cortex, CA1 and CA2/3 to normal level.

The present study showed cognitive deficits in the novel object recognition task in male rats receiving sub-chronic PCP administration. This result represented a consistency with other studies using both male[17] and female rats[5]. Cognitive deficit was also found in sub-chronic PCP administration rat using other tasks such as reversal learning[18] and attentional set shifting[19]. Therefore, sub-chronic PCP administration to animal could be a valuable method to model cognitive deficit found in schizophrenia.

In the present study, the cognitive deficit found in novel object recognition task was attenuated by administration of Brahmi although it could not recovery to normal. These results were interpreted as cognitive enhancement effect of Brahmi in schizophrenia-like psychosis. Consistent with these findings, other animal studies have shown that Brahmi could increase learning and memory task and also prevented age-associated neurodegeneration[20,21]. Recent studies in humans have suggested that Brahmi extract is a potential cognitive enhancer and neuro-protectant against Alzheimer's disease[22].

Immunohistochemical analysis in sub-chronic PCP administration revealed a significant increase in

NMDAR1 neuronal density in the prefrontal cortex, CA1 and CA2/3. These results suggested that sub-chronic PCP administration appeared to have an effect on NMDAR1 up-regulation in the brain regions that mainly contribute to cognitive function and memory. Consistent with these results, several studies have shown NMDA up-regulation after PCP administration in the rat hippocampus[23]. Additionally, a previous study in schizophrenic patients also found NMDA receptor up-regulation in post-mortem putamen and temporal cortex[8], which was interpreted as a receptor up-regulation in response to glutamatergic hypofunction.

It has been reported that PCP-induced NMDA receptor up-regulation could produce neurotoxicity and neuronal cell death[24], which lead to cognitive deficit and behavioral disorders[25]. Therefore, NMDAR1 receptor up-regulation observed in the present study may induce the neuronal cell death, which might be implicated in cognitive deficit found in schizophrenia.

Similar to the findings from the object recognition task, increase in NMDAR1 neuronal density in the prefrontal cortex, CA1, and CA2/3, was absolutely attenuated by administration of Brahmi. As previously discussed, Brahmi extract has been reported as a potential cognitive enhancer and neuroprotectant[22]. Findings from the present study support a cognitive enhancement effect of Brahmi against PCP-induced NMDAR1 up-regulation in the prefrontal cortex, CA1, and CA2/3 of the schizophrenic rat model.

Conclusion

While sub-chronic administration of PCP produces cognitive deficits in novel object recognition task and NMDAR1 up-regulation in the prefrontal cortex and CA1-3 of hippocampus, administration of Brahmi provides a cognitive enhancement effect against these behavioral deficit and NMDAR1 up-regulation. Therefore, Brahmi could be a valuable alternative medicine against cognitive impairment in the PCP administered rat model of schizophrenia and to some extent, the psychotic patients.

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Potential conflicts of interest

None.

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ฤทธิ์กระตุ้นการเรียนรู้และความจำของ Bacopa monnieri (พรมมิ) ต่อการแยกแยะวัตถุใหม่ และต่อปริมาณของตัวรับชนิด NMDA ในสมองส่วน prefrontal cortex และ hippocampus ในหนูที่ถูกเหนี่ยวนำให้เป็นโรคจิตเภทด้วย sub-chronic phencyclidine

ปริศนา ปียะพันธุ์, ธนิศรา เวชเตง, สีวบูรณ์ สิรีรัฐวงศ์

ภูมิหลัง: *การเรียนรู้และความจำบกพร่องเป็นอาการที่พบได้ทั่วไปในโรคจิตเภทซึ่งไม่สามารถรักษาได้ด้วยยาในกลุ่ม antipsychotics พรมมิซึ่งเป็นที่รู้จักกันอย่างแพร่หลายในการช่วยกระตุ้นการเรียนรู้และความจำอาจเป็นแนวทางใหม่ของการรักษาการเรียนรู้และความจำที่ลดลงในโรคจิตเภท*

วัตถุประสงค์: *เพื่อศึกษาผลของพรมมิต่อการเรียนรู้และความจำที่ลดลงและต่อปริมาณของตัวรับชนิด NMDA ในสมองของหนูที่ถูกเหนี่ยวนำให้เป็นโรคจิตเภทด้วย sub-chronic phencyclidine (PCP)*

วัสดุและวิธีการ: *หนูได้รับ PCP หรือ vehicle ครึ่งหนึ่งของหนูที่ได้รับ PCP ได้รับการป้อนพรมมิ ค่า discrimination ratio (DR) แสดงถึงความสามารถในการเรียนรู้และความจำได้มาจากการทดสอบการแยกแยะวัตถุใหม่ (novel object recognition) การวัดปริมาณของตัวรับชนิด NMDA ในสมองส่วน prefrontal cortex, striatum, cornu ammonis fields 1-3 (CA1-3) และ dentate gyrus (DG) ใช้วิธี immunohistochemistry*

ผลการศึกษา: *DR ในหนูกลุ่มที่ได้รับ PCP มีค่าลดลงเมื่อเทียบกับหนูกลุ่มควบคุม การลดลงของ DR ในหนูที่ได้รับ PCP นี้เกิดขึ้นร่วมกับ NMDA up-regulation ในสมองส่วน prefrontal cortex และ CA1-3 แต่ไม่พบในสมองส่วน striatum และ DG หนูกลุ่มที่ได้รับ PCP ร่วมกับพรมมิมีค่า DR เพิ่มขึ้นเมื่อเทียบกับกลุ่มที่ได้รับ PCP อย่างเดียว การเพิ่มขึ้นของ DR ในหนูกลุ่มที่ได้รับ PCP ร่วมกับพรมมินี้เกิดขึ้นร่วมกับการลดลงของ NMDA ในสมองส่วน prefrontal cortex และ CA1-3 ปริมาณของ NMDA ในสมองของหนูที่ได้รับ PCP ร่วมกับพรมมิไม่แตกต่างจากหนูกลุ่มควบคุม*

สรุป: *การเรียนรู้และความจำที่ลดลงในหนูที่ได้รับ PCP เกิดขึ้นจาก NMDA up-regulation ในสมองส่วน prefrontal cortex และ CA1-3 เป็นที่น่าสนใจว่าพรมมิสามารถฟื้นฟูการเรียนรู้และความจำที่ลดลงนี้ได้โดยการลดปริมาณ NMDA ในสมองส่วนดังกล่าวนี้ให้กลับสู่ปกติ*