The role of β-phenylethylamine in behavioral sensitization

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The role of β-phenylethylamine in behavioral sensitization

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The Master's Thesis submitted
to the Department of Medical Science,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the
degree of Master of Medical Science

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December 2007

This certifies that the Master's Thesis
of Hye Kyoung Park
is approved.

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Yonsei University

December 2007

Acknowledgements

First of all, I would especially like to thank my advisor, Dr. Jeong-Hoon Kim. He inspired me to make a study of neuroscience and especially of drug addiction. He continually stimulated me to develop scientific thinking, writing as well as research skills. Whenever I faced lots of difficulties which arose throughout my master's course, he always encouraged me to overcome them and gave me many opportunities to solve problems by myself. In fact, it would not have been possible to complete this work without his enthusiastic guidance. I would also like to thank my dissertation committee, Dr. Dong Goo Kim and Dr. Kee Namkoong, for their helpful guidance and comments throughout this project.

I am also very grateful for being with my colleagues in the Kim's laboratory and wish to thank Seungwoo Kim, Wha Young Kim, Hyung Shin Yoon, Ju Kyong Jang, So Ra Shin for their help, encouragement, and friendship. And I extend my thanks to all the people in the Department of Physiology.

There is no way to thank my family enough. They deserve my deep warm and special acknowledgement for their love and care. My parents have always been a constant supporter not only for materials but also for spiritual encouragement throughout my life.

And thanks God.

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Abstract

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Beta-phenylethylamine (PEA) is an endogenous trace amine that is found in central nervous system (CNS). It is structurally related to amphetamine (AMPH) and has amphetamine-like behavioral effects when injected into rodents in large doses. For example, it was previously shown that PEA-induced stereotyped behavior in rats was gradually increased by repeated daily administration of PEA for 28 days, suggesting that behavioral sensitization to PEA may occur. In addition, various behavior induced by PEA appeared to involve release of monoamines, suggesting that the biochemical properties of PEA are closely related to those of AMPH. In the present study, we investigated whether chronic treatment with PEA induces behavioral sensitization to AMPH challenge in rats. Male Sprague-Dawley rats were randomly divided into four treatment groups. Rats were administered with five injections, one injection every second or third day, of either saline, PEA (10 or 50 mg/kg, i.p.) or AMPH (1.5 mg/kg, i.p.). One week after the last injection, all of the animals received an amphetamine (1.0 mg/kg, i.p.) challenge and then their locomotor responses were assessed for an hour. It was found that pre-treatment with PEA (50 mg/kg, i.p.) produced locomotor

sensitization to amphetamine, but not vice versa. Next, in order to identify the role of group Ⅱ metabotropic glutamate receptors, we measured locomotor activity in PEA pre-exposed rats after a challenge with group Ⅱ mGluR antagonist LY341495 (1.0 mg/kg, i.p.) or agonist LY379268 (1.0 mg/kg, i.p.). Rats previously exposed to PEA compared to saline showed a greater locomotor response to LY341495, while these effects were not present when LY379268 was injected. Taken together, our results indicate that PEA may play a role in the development, but not in the expression, of locomotor sensitization to AMPH. Further, they suggest that group Ⅱ mGluR may have the important role in this process.

Key words : β-phenylethylamine, behavioral sensitization, metabotropic glutamate receptor, amphetamine

The role of β-phenylethylamine in behavioral sensitization

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I. INTRODUCTION

Drug abuse is defined as overwhelming involvement with the use of a drug (compulsive use) and includes a number of symptoms or criteria that reflect a loss of control over drug intake[1]. It is known to be mediated by rewarding circuit in the brain. This circuit includes ventral tegmental area (VTA), nucleus accmbens (NAcc), prefrontal cortex (PFC), which have major roles in the drug abuse[2]. Interestingly, it has been shown that repeated intermittent exposure to psychomotor stimulant drugs such as amphetamine (AMPH) and cocaine leads to a long lasting enhancement in locomotor responding to these drugs, a phenomenon known as locomotor sensitization[3]. This phenomenon has been used as an animal model to understand drug abuse, and VTA and NAcc are important neuronal substrates mediating it.

β-phenylethylamine (PEA) is an endogenous trace amine that is found in mammalian brain with highest levels in regions such as the caudate-putaman, olfactory tubercles, and NAcc[4]. Both structurally and behaviorally, PEA is similar with a psychostimulant drug amphetamine (AMPH) and has been implicated in human psychiatric disease like depression and schizophrenia, leading to propose it to be called as an 'endogenous AMPH'[5].

Repeated intermittent administration of AMPH produces locomotor sensitization, which is a proposed model for the escalation of drug use and craving characteristic of human addicts[6]. The development of locomotor sensitization by drugs like AMPH can be separated as two phase of induction and expression, in which different neuronal processes involved mediating distinct neuronal substrates in the brain[7,8]. It has been reported that PEA increases locomotor activity in rodents similar to AMPH but with the less potency and duration of action[9-11]. Interestingly, it has been also shown that more than 21 days of daily systemic PEA administration produces locomotor sensitization to the challenges of AMPH as well as of PEA itself[12,13]. And local application of PEA has increased extracellular levels of dopamine in the striatum, NAcc, as well as in the VTA[14-16]. These evidences suggest that endogenous PEA may have the ability to similarly act as psychostimulants. Moreover, due to recent identifications of receptors that are specifically activated by PEA, it has become interesting to newly find the role of PEA related to drug abuse in the CNS[17,18]. However, early findings of locomotor sensitization by PEA were developed with very heavy amount of it compared to that of AMPH, and also the effect of PEA challenge on the expression of locomotor sensitization developed by AMPH pre-exposure has not been tested yet. Thus, we examined in the present study that the expression of locomotor sensitization with AMPH challenge after a mild chronic PEA treatment, and vice versa, with a pre-exposure scheme of just several times of intermittent

injection.

Metabotropic glutamate receptors (mGluRs) are widely expressed in rat brain. And the role of mGluRs in psychostimulant-induced behavioral sensitization has been studied. For example, repeated co-infusion with AMPH into the VTA of the broad spectrum mGluR antagonist, (RS)-α-methyl-4-carboxyphenylglycine [(RS)-MCPG], has been shown to prevent the development of locomotor sensitization by AMPH[19], while the group Ⅱ mGluR-selective antagonist LY341495 elicits a greater locomotor response in AMPH compared to saline pre-exposed rats[20]. More recently, it was shown that microinjected LY341495 into the NAcc also enhanced the increase of locomotor activity in AMPH compared to saline pre-exposed rats[21]. These previous results indicate that group Ⅱ mGluR-mediated neuronal plasticity may have involved in the expression of AMPH-induced locomotor sensitization. Although PEA has some similarity with AMPH, because this effect has not been examined yet for PEA, we further investigated the contribution of group Ⅱ mGluRs to PEA-induced locomotor sensitization.

II. MATERIALS AND METHODS

1. Subjects and surgery

Male Sprague-Dawley rats weighing 230-260g on arrival from Samtako (Osan, Korea) were used. They were housed three per cage in a 12-h light/dark cycle room with food and water available at all times. All procedures were conducted according to an approved IACUC protocol.

2. Drugs

PEA hydrochloride (Sigma Chemical, St. Louis, MO, USA) and d-AMPH sulfate (U.S.P., Rockville, MD, USA) were dissolved in sterile 0.9% saline. Group Ⅱ mGluR antagonist LY341495 (Tocris, Ellsville, MO, USA) and agonist LY379268 (Tocris, Ellsville, MO, USA) were dissolved in 1.2 equivalent of NaOH solution and small aliquots were stored at -70℃ prior to use. Their doses refer to the weight of the salt.

3. Locomotor activity

Locomotor activity was measured in a bank of 6 activity boxes (35 X 25 X 40 cm) (IWOO Scientific Corporation, Seoul, Korea). Each box was made of translucent Plexiglas and individually kept in Larger PVC plastic sound attenuating cubicles. The floor of each box consisted of 21 stainless steel rods (5mm diameter) spaced 1.2cm apart center-to-center. Two infrared light photocells (Med Associates, St. Albans, VT, USA) positioned 4.5cm above the floor and spaced evenly along the longitudinal axis of the box estimated locomotor activity.

4. Design and procedure

Animals were treated for experimental procedures as follows. All experiments consisted of a pre-exposure and a test phase for sensitization.

Experiment 1 : During pre-exposure phase, different four groups of rats were administered systemic injection of either saline, PEA (10 or 50 mg/kg), or AMPH (1.5 mg/kg) every 2 to 3 days for a total of five times. This regimen of AMPH injection is known to produce enduring sensitization of the locomotor response to AMPH[3,19]. Immediately after the first and fifth injections, rats were placed in the activity boxes and their locomotor activities were measured for 1 h. And rats were home cage-injected for the rest of days during this drug pre-exposure phase. A week of drug-free withdrawal period after the last injection, they were first habituated to the activity boxes for 1 h and then all AMPH (1.0 mg/kg, i.p.) challenged, then immediately returned to the activity boxes and their locomotor activities were measured for 1 h.

Experiment 2 : Additional three groups of rats, administered systemic injections of either saline, PEA (50 mg/kg), or AMPH (1.5 mg/kg), followed the same pre-exposure treatments as above. A week after the last injection, they were all PEA (50 mg/kg, i,p.) challenged and their locomotor activity measured for 1 h.

Experiment 3 : For pre-exposure, rats were administered five injections of either saline or PEA (50 mg/kg, i.p.), one injection every second or third day. A week after last injection, they were challenged with injections of LY341495 (1.0 mg/kg, i.p.) or LY379268 (1.0 mg/kg, i.p.) and then locomotor activities measured for 1 h. Rats were always first habituated to the activity boxes for 1 h before drug injection given.

5. Data analyses

Total locomotor activity scores (means ± s.e.m.) were analyzed by using two-way ANOVA with injections and groups as factors of variation. Post hoc Scheffè or Student-Newman-Keuls comparisons were made according to Kirk(1968)[22].

III. RESULTS

1. Repeated exposure to β-phenylethylamine produces locomotor sensitization to amphetamine.

Figure 1A shows the locomotor activity count obtained in rats systemically injected with either saline, one of two doses of PEA (10 or 50 mg/kg) or AMPH (1.5 mg/kg) during pre-exposure phase. The two way-between within ANOVA conducted on these data revealed multiple significant effects of different pre-exposure groups [$F(3,34)=83.91$, $p<0.001$], days [$F(1,34)=9.98$, $p < 0.004$] and a group x days interaction [$F(3,34)= 8.12$, $p<0.001$]. As expected, acute injection of AMPH to that of saline significantly increased locomotor activity response on day 1 and these effects were further enhanced when measured on day 5 ($p<0.001$). Acute injection of PEA, however, produced no effects on locomotor activity both on day 1 and on day 5. After a week of drug-free withdrawal period, AMPH compared to saline pre-exposed group of rats showed again a sensitized locomotor activity to AMPH challenge. Interestingly, those PEA compared to saline pre-exposed also showed a sensitized locomotor activity to this challenge (Fig.1B). The ANOVA counted on these data showed significant effect of groups [$F(3,34)=5.65$, $p<0.004$]. *Post hoc* Scheffè revealed that significant effects appeared on high dose of PEA and AMPH ($p<0.05$-0.01). Time-course data in Fig. 1C shows that the sensitized locomotor responses to AMPH challenge in PEA pre-exposed rats persisted apparently for up to the 40 min of testing similar to AMPH.

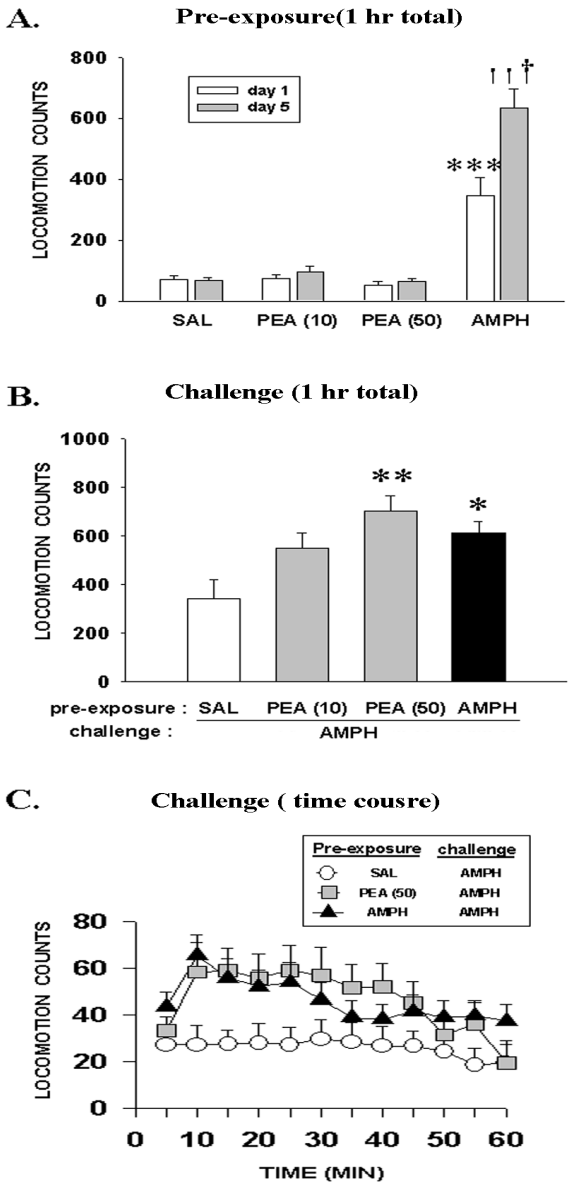

Figure 1. Repeated exposure to β-phenylethylamine (PEA) produces locomotor sensitization to amphetamine (AMPH) challenge. Date are illustrated as group mean (+SEM) locomotor activity counts obtained for 1 h following the drug injection during the pre-exposure period (A) and at the time of challenge (B). Time-course data at the challenge (C) are shown for only three groups of the

four tested to clarify the effects of high dose of PEA. Numbers of rats in each group are 9 to 10. Symbols indicate significant differences as revealed by *post-hoc* Scheffè comparisons following two-way between-within (for pre-exposure) and one-way (for challenge) ANOVA's. *** p < 0.001 ; AMPH compared with saline pre-exposed on day 1. ** p <0.01, * p < 0.05;PEA (50mg/kg) or AMPH compared with saline pre-exposed after AMPH challenge. † † † p <0.001 ; Day 5 compared with day 1 in rats AMPH pre-exposed.

2. PEA challenge has no effect on the expression of locomotor sensitization developed by either AMPH or PEA itself.

On the contrary, we examined the role of PEA challenge on the expression of locomotor sensitization developed by AMPH or PEA itself. In this separate experiment, when challenged with PEA, rats pre-exposed a week earlier to either PEA (50 mg/kg) or AMPH showed locomotor activity that was not different from that displayed by saline pre-exposed rats. In addition. PEA produced no effects on locomotor activity both acutely on day1 and repeatedly on day 5 as well. (data not shown) The ANOVA conducted on these data showed no significant effects of groups [$F_{(2,15)}$=0.09, p<0.92].

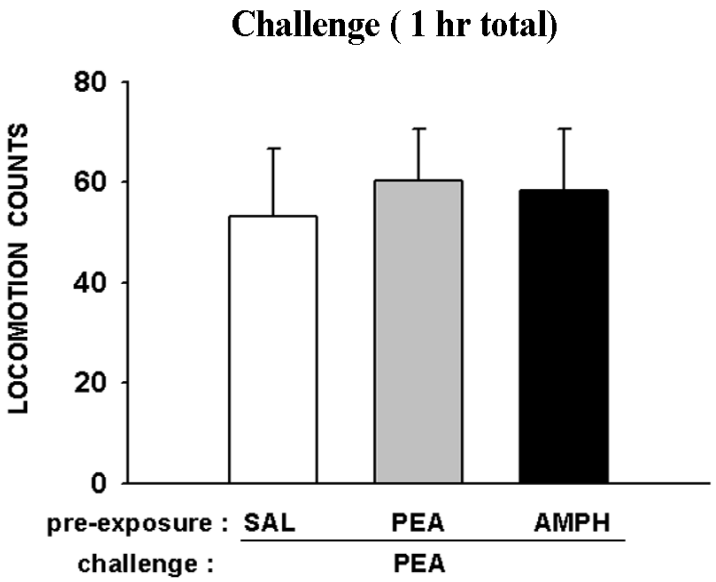

Figure 2. PEA challenge has no effect on the expression of locomotor sensitization developed by repeated exposure to either amphetamine (AMPH) or β-phenylethylamine (PEA) itself. Date are illustrated as group mean (+SEM) locomotor activity counts obtained for 1 h following the drug injection at the time of challenge(n=6/group).

3. The group Ⅱ mGluR antagonist LY341495 produced enhanced locomotor activity in rats previously exposed to PEA but not to saline.

We examined the contribution of group Ⅱ mGluRs to PEA-induced locomotor sensitization by measuring their locomotor activities. When challenged with LY341495 (1.0 mg/kg, i.p.) 1 week following the last drug pre-exposure injection, it was found that this selective group Ⅱ mGluR antagonist produced increased locomotion (Fig. 3). This effect was absent in rats tested with the selective group Ⅱ mGluR agonist LY379268, confirming that LY341495 increased locomotor activity.

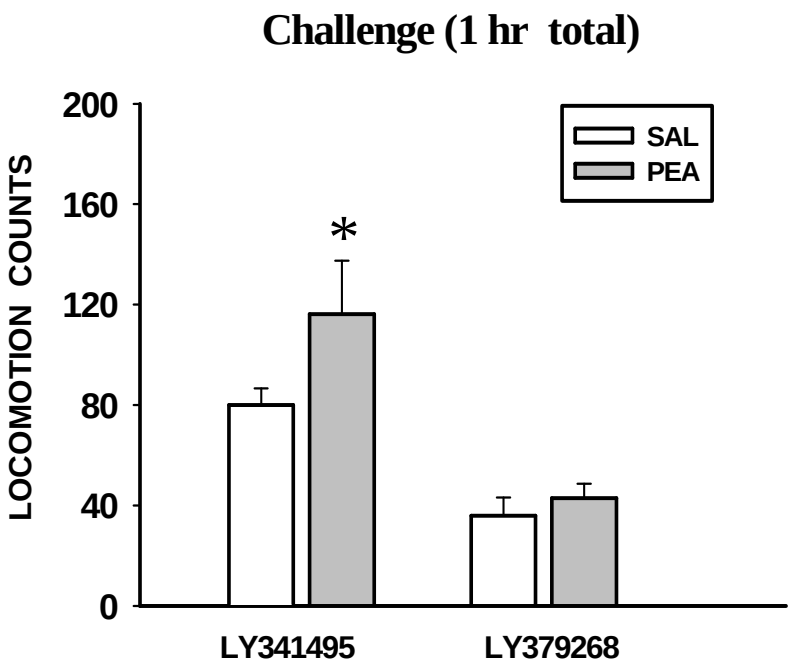

Figure 3. LY341495 produces enhanced locomotor activity in β -phenylethylamine (PEA) pre-exposed rats. Data are illustrated as group mean (+SEM**)** locomotor activity counts obtained for 1 h at the time of challenge. A symbol indicates significant difference as revealed by Student-Newman-Keuls comparisons following two-way ANOVA's. * $p < 0.05$: PEA compared with saline pre-expose rats with LY341495 challenge.

IV. DISCUSSION

In the present experiment, repeated exposure to PEA produced the locomotor sensitization to amphetamine, but not vice versa, in the rat. In addition, the group Ⅱ mGluR antagonist LY341495 increased locomotor activity in rats previously exposed to PEA but not to saline. Taken together, these findings suggest that endogenous PEA may play an important role in the induction, but not in the expression, of locomotor sensitization, and these effects may be mediated by group Ⅱ mGluRs.

1. PEA produces locomotor sensitization to AMPH challenge.

It was previously shown that acute injection of PEA did not significantly stimulate locomotor activity in rat[12], but daily injections of PEA resulted in the development of stereotyped behaviors[23]. It has also shown that more than 21 days of daily chronic PEA injections develop behavioral sensitization to the challenges of AMPH as well as of PEA itself[12,13]. However, the time that required for this sensitization to PEA to develop was very long, and the amount of PEA used was very heavier compared to those of AMPH generally used in the procedure of developing AMPH-sensitization. The present study found, interestingly, that only several times of intermittent PEA injections are enough to induce locomotor sensitization which is evoked by AMPH challenge after a week of withdrawal. As mentioned above, the locomotor sensitization consists of two phases; induction and expression[7,8]. In this regard, our findings suggest that PEA may have a major role in the induction, but not in the expression, phase of locomotor sensitization in the AMPH challenged rat.

2. PEA challenge has no effect on the expression of locomotor sensitization developed by repeated exposure to either AMPH or PEA itself.

Figure 2 shows that AMPH or PEA pre-exposure procedures did not evoke sensitized locomotion to PEA challenge contrary to the previous studies, suggesting that PEA-induced locomotor sensitization may require the heavier pre-exposure , daily over 21 days, to express its development to PEA itself[12]. And the same dose of PEA (50 mg/kg), which is enough to induce locomotor sensitization revealed by AMPH challenge a week after as shown in Figure 1 , is not able to evoke the expression of locomotor sensitization induced by AMPH pre-exposure. This result indicates that PEA challenge has no effect on the expression phase of locomotor sensitization induced by repeated exposure to either AMPH or PEA itself. Taken together, this study suggests that the major role of PEA in the locomotor sensitization is in the induction, not in the expression of it.

3. The group Ⅱ mGluR antagonist LY341495 produced enhanced locomotor activity in rats previously exposed to PEA but not to saline.

Considering that PEA is an endogenous trace amine with a rapid metabolic turnover due to the easy degradation by monoamine oxidase type B[24], it is very interesting that locomotor sensitization is observed a week drug free withdrawal after the last PEA injection. This fact suggests that the augmentation of AMPH-induced locomotor sensitization after repeated exposure to PEA is ascribed not to the accumulation of PEA in the rat brain, but to the enhancement of the neuronal response to PEA treatment at the time of the induction of locomotor sensitization. The induction and the expression of locomotor sensitization by psychostimulant drug has been

accompanied by mGluRs, especially group Ⅱ mGluR[19,25]. Therefore, in the present study, we examined whether the effect of PEA on the locomotor sensitization may be due to contribution of mGluRs.

In the previous experiments, the group Ⅱ mGluR antagonist LY341495 increased locomotor activity when administered systemically to rats previously exposed to AMPH but not to saline. This effect was observed only with LY341495, but not with the agonist LY379268[21]. These findings indicate that AMPH pre-exposure produces neuronal plasticity involving group Ⅱ mGluRs, consequently resulting in the increase of locomotor activity. Interestingly, when administered systemically, LY341495 (1.0 mg/kg, i.p.) also produced significant increase in locomotor activity in rats pre-exposed to PEA similar to AMPH pre-exposures. However, these effects were not observed when LY379268 was injected. Given the above evidence, it is noteworthy that repeated exposure to PEA alters glutamatergic neurotransmission mediated by group Ⅱ mGluRs and these receptors are well positioned to modulate the expression of PEA-induced locomotor sensitization.

Ⅴ.CONCLUSION

We examined the role of PEA in the locomotor sensitization by measuring locomotor activities in the PEA pre-exposed rats with challenge of AMPH, and vice versa. Also, group Ⅱ mGluR ligands were tested to examine whether the PEA-induced locomotor sensitization may involve these receptors. The results obtained are summarized as follows.

1. Repeated exposure to PEA produces locomotor sensitization to AMPH.

2. PEA challenge has no effect on the expression of locomotor sensitization developed by repeated exposure to either AMPH or PEA itself.

3. The group Ⅱ mGluR antagonist LY341495 produced enhanced locomotor activity in rats previously exposed to PEA but not to its agonist LY379268.

The present results suggest that endogenous PEA may play an important role in the induction, but not in the expression, of locomotor sensitization, and this locomotor change may result from the altered glutamatergic transmission mediated by group Ⅱ mGluRs.

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Abstract (in Korean)

β-phenylethylamine(PEA)의 행동과민반응에서의 역할

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박 혜 경

수년간의 연구를 통하여 약물 중독은 대뇌에서 소위 보상경로(reward pathway)라고 알려진 부위를 통하여 매개됨이 알려졌다. 대뇌보상경로는 주로 중뇌에 위치한 복측피개(VTA)와 전뇌의 측좌핵(NAcc) 그리고 전전두엽피질(PFC)을 중심으로 연결 되어진 신경 경로를 가리키는데, 이들 부위에서 분비되는 신경전달 물질인 도파민과 글루타메이트는 각각 약물 중독에 있어서 매우 중요한 역할을 하고 있음이 밝혀지고 있다. 약물에 의한 도파민과 글루타메이트 신경 전달은, 지속적인 신경 가소성적 변화들을 일으키게 되는데 이것은 약물 중독의 중요한 특징 가운데 하나인 행동과민반응(Behavioral sensitization)을 유도하게 된다. 행동과민반응은 cocaine이나 AMPH과 같은 중독성 약물을 동물에게 반복하여 주게 되면 그 약물에 대한 행동반응이 증가되어 나타나는 현상을 일컫는데, 약물 중독을 이해하는 동물 모델로 많이 연구되어지고 있다.

최근 들어 우울증이나 정신분열증과 같은 정신 질환 연구에서 생체 내 trace amine과의 관련성이 보고됨에 따라, 이에 대한 관심이 커지고 있다. Trace amine은 대뇌에 소량으로 존재하며 도파민, 세로토닌과 같이 널리 알려진 전형적인 생체 아민과 기능적으로 연관이 있다고 여겨지는데, 그 중에서도 베타 페닐에틸아민(PEA)은 중독성 약물인 AMPH과 여러 가지 유사성을 가지고 있는 것으로 보고되고 있다. 가령 설치류에게 높은 농도

로 주사하였을 때, AMPH과 유사한 행동 변화를 가져 오며, 21일 이상의 장기 투여 시에는, 행동과민 반응이 유도 된다는 보고가 있었다. 이는 생체 내에 존재하는 PEA가 AMPH과 같이 약물 중독에도 관련되어 있을 가능성을 보여 준다. 따라서 본 연구에서는 1) 백서에게 PEA를 반복적 간헐적으로 복강에 전 처리 한 뒤, 약물이 없는 (withdrawal) 기간을 일주일 지난 후, AMPH을 복강에 주입하였을 때 어떤 행동의 변화가 일어나는지, 2) 그리고 PEA 또는 AMPH을 반복적 간헐적으로 복강에 처리한 뒤, 위와 마찬가지로 약물 없는 기간을 일주일 지난 후에, PEA를 복강에 주입하였을 어떤 변화가 일어나는지 알아보고, 마지막으로 3) 앞서의 변화들이 어떤 경로를 통해 일어나는지 알아보기 위해, 이미 행동과민반응에서 중요한 역할을 한다고 알려져 있는 group Ⅱ mGluR의 길항제 LY341495를 사용하여, 반복적 간헐적으로 주입한 PEA에 의해 유도된 행동과민반응이 무엇을 경유하여 일어나는지 확인하고자 한다.

이 실험 결과를 통해 PEA를 전 처리한 집단에 일주일 후 AMPH을 처리하였을 때, saline을 전 처리한 집단에 비해, 행동 반응이 현저하게 증가되어 나타나는 현상을 발견 할 수 있었으며, 이는 AMPH으로 유도되는 행동과민반응과 흡사함을 알 수 있었다. 그러나 흥미롭게도 PEA를 전처리하거나 AMPH를 전처리 하고 일주일 후에, PEA를 처리한 경우에는, 각 그룹간의 행동 차이가 발견되지 않는 것을 확인 하였다. 이러한 결과는 PEA가 AMPH에 대해 나타나는 행동과민반응에 있어서 발현(expression)단계 보다 발달(induction)단계에서 더 중요한 역할을 하고 있음을 보여준다. 한편, 이와 같이 PEA의 전처리에 의하여 AMPH으로의 행동과민반응이 나타날 때 group Ⅱ mGluR이 중요한 역할을 할 수 있음을 관찰하였다. 이상의 결과들을 통하여 생체내의 PEA는 AMPH과 유사하게 행동과민반응의 유도에 어떤 역할을 하고 있으며, 이 때 mGluR을 통한 glutamatergic neurotransmission이 관여하고 있음을 알 수 있다.

핵심 되는 말 : β-phenylethylamine (PEA), 행동과민반응, 암페타민, Metabotropic glutamate receptor (mGluR)