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원 저

# Acupuncture Attenuates Cocaine-induced Dopamine Release in the Nucleus Accumbens and Voluntary Cocaine Intake in Rats

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## 국문초록

# 침자극이 코카인 투여로 인한 측핵내 도파민 유리와 자발적 코카인 섭취량에 미치는 효과

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***목적*** : 침(鍼)은 정신이상 및 약물중독과 같은 많은 기능상의 장애질환을 치료, 조정하는데 널리 쓰이고 있으며, 중추신경계에서 생화학적인 균형을 유지하는데 기여한다고 밝혀져 있다. 동물 연구에서 코카인의 강화 및 민

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감화 특성과 중추의 도파민 활성과의 관련 가능성이 높아지고 있다. 본 연구에서는 약물중독 치료에 이용할 수 있는 침의 효과를 규명하기 위하여 침자극 후 급성 코카인 투여에 의한 도파민 유리 및 자발적 코카인 섭취량에 미치는 침자극의 효과를 측정하였다.

***방법*** : 웅성 SD 쥐에 코카인 (1mg/kg, i.v.)의 주사 직전 양측의 신문혈(HT7)을 1분간 침자극 한 후, 측핵내 세포외액의 도파민 및 대사산물의 함량변화를 미세투석법을 이용하여 HPLC로 분석하였다. 침자극 후 two-bottle, free choice protocol을 이용하여 자발적 코카인 섭취량의 변화를 관찰하였다. 별도의 쥐를 이용하여 1회 동량의 코카인 정맥주사하고 2주간의 철회를 거친 다음 two-bottle, free choice protocol을 실시하여 자발적 코카인 섭취량과 급성 코카인 투여 후 측핵 중 도파민유리증가율 사이의 상관관계를 조사하였다.

***결과*** : 신문혈(HT7) 자침이 코카인 1회 주사 후에 유도된 도파민 증가를 대조혈(내관혈(PC6), 또는 꼬리)에 비해 유의하게 억제하였으며 two-bottle choice protocol에 의한 동물의 자발적 코카인 섭취량을 억제하였다. 아울러 자발적 코카인 섭취량과 급성 코카인 투여 후 측핵 중 도파민유리증가율 사이에는 상관관계가 있었다.

***결론*** : 본 실험결과 침자극에 의해 자발적 코카인 섭취량이 억제되는 것은 측핵에서의 도파민 유리억제에 의해 중개되는 것으로 보여지므로 침자극은 코카인중독과 같은 약물의 중독치료에 이용될 수 있을 것으로 사료된다.

***Key words*** : *Cocaine, acupuncture, nucleus accumbens, dopamine, voluntary cocaine intake*

# Ⅰ. Introduction

Cocaine is a drug with very potent reinforcing properties. Based largely on animal self-administration studies, the reinforcing effects of cocaine have been linked to central dopamine (DA) activity. Moreover, there is considerable evidence implicating the mesocorticolimbic DA system, specially the nucleus accumbens(NAC) and the ventral tegmental area(VTA). The most compelling evidence for a central role of the mesocorticolimbic DA system in the reinforcing actions of cocaine includes the observations that DA-depleting lesions of the NAC or VTA attenuate cocaine self-administration and that DA antagonists block and DA agonists facilitate the reinforcing effects of self-administered cocaine. Central DA activity is also associated with the locomotor activity[1)~3)].

Acupuncture as a therapeutic inter-vention has been widely practiced in the United States and eastern countries. Studies in animals and humans have demonstrated that acupuncture can cause multiple biological responses that occur locally and at a distance[4)]. Especially, a large number of studies have been undertaken to investigate acupuncture analgesia and the discovery of the participation of the central endorphin system was a great step toward understanding the analgesic effect of acupuncture[5)]. In addition, it has been noted that acupuncture contributed to the biochemical balance in the central nervous system and played a role

in regulating neurotransmitters that control health and disease[6)~8)].

The efficacy of acupuncture in the treatment of substance abuse and drug withdrawl has been demonstrated to the scientific community. While acupuncture is still regarded with skepticism, clinical trials and scientific investigations have proven its effectiveness. In fact, acupuncture has become standard procedure in many detoxification programs worldwide[9),10)]. However, few experiments using animal model have been performed an the mechanism underlying the effectiveness in the treatment of cocaine abuse.

In oriental medicine, Shenmen(HT7) on the heart channel is the point used to treat mental and psychosomatic disorders and known clinically to produce a sedation effect[11)].

This study was designed to establish whether acupuncture was effective in the reinforcing action of cocaine and whether dopamine response which is known to be associated with cocaine abuse is effected by acupuncture at HT7.

## Ⅱ. Materials and methods

### 1. Subjects

Male Sprague-Dawley rats weighing 270~310g were obtained from Daehan Animal Corp. (Seoul, Korea/SPF animals). Rats were kept on ad libitum food and water and maintained on a 12h light-dark cycle throughout the course of study.

### 2. Surgery

Rats were anesthetized with sodium pentobarbital(50mg/kg body weight, i.p.). Microdialysis probe guide cannulae were implanted during a stereotaxic surgical procedure using the following coordinates ; nucleus accumbens(AP 1.7, ML 0.8, DV 6.0) according to the atlas of Paxinos and Watson[12)]. One week after placement of guide cannulae, the PE 50 polyethylene catheter was put into the right external jugular vein for injection of cocaine. Catheters were plugged and exteriorized via a skin incision in the back of the neck. Catheter patency was maintained by flushing the catheter with 0.5ml heparinized saline(500U/ml) twice a day.

Experimental observations were usually started 24 hours after rats had fully recovered.

### 3. Microdialysis

Microdialysis probes(CMA/11, Cuprophane dialysis membrane, 6000 Dalton, 2mm length) were inserted throughout the guide cannulae into the brain of unanesthetized rats. The microdialysis fluid was perfused at a rate of 1.5 $\mu$l/min(CMA/100 Microinjection Pump) throughout all experiments. The microdialysis fluid was a modified Ringer's solution containing 150 mM NaCl, 3.0mM KCl, 1.4mM $CaCl_2$, 0.8mM Mg $Cl_2$ in 10mM phosphate buffer at pH 7.1. Samples were collected at 10-min intervals 2 hours after initiation of perfusion and injected directly into an HPLC apparatus. On completion of an

experiment, rats were sacrificed and brains were prepared for histology to confirm the location of the microdialysis probe.

## 4. Determination of dopamine and its metabolites

Microdialysates were analyzed using HPLC with a reverse-phase column(HR-80, 80×4.6 mm, 3㎛ particle size ; ESA) and a coulometric detector(ESA, Coulochem II, Model 5200A with analytical cell, Model 5014B, Guard Cell Model 5020). A guard cell was set at 400mV and the screen electrode was set at -100mV with the detection electrode act at 320mV. The composition of mobile phase was 75mM sodium phosphate monobasic, 1.7mM sodium octane sulfonate, 25㎛M EDTA, 0.714mM triethylamine and 10% acetonitrile, pH 3.0. The mobile phase was pumped with an Sykam 7121 pump at a flow rate of 1.0 ml/min. The sensitivity of the assay for DA was 5 fmol per sample.

## 5. Experimental protocol

Before use in vivo, microdialysis probes were calibrated in vitro by dialysis. Probe recovery values were used to normalize microdialysate dopamine, DOPAC and HVA concentration, and all reported results are based on levels corrected for individual probe recovery. Baseline levels of dopamine were defined as the average value in three consecutive sample with less than 10% variation. Following the estabilishment of baseline dopamine levels, animals were given an intravenous injection of cocaine hydrochloride(1mg/kg) dissolved in saline. Animals received acupuncture for 1min at points corresponding to bilateral HT7 and bilateral PC6 and tail as control points before an intravenous injection of cocaine hydrochloride. The stimulation was delivered by twisting acupuncture needles while needles were inserted to acupoints and withdrawn from acupoints.

The anatomical location of acupuncture points stimulated is described as follows[11].

• Shenmen(HT7) : On the transverse crease of the wrist, radial to the tendon of the m. flexor carpi ulnaris.

• Neiguan(PC6) : Between the tendons the m. palmaris longus and flexor carpi radialis

Rats were immobilized by grabbing while acupuncture was given. Therefore, we studied the effect of immobilization stress on extracellular dopamine response to cocaine. No significant difference was found between freely moving rats and immobilized rats in extracellular dopamine responses to cocaine. Freely moving rats were used to study the correlation between voluntary cocaine intake and cocaine-induced elevation of extracellular dopamine levels in the nucleus accumbens. The animals were returned to home cages in which they were individually housed after the microdialysis study. Following a two week "wash-out"period, rats were entered into a two-bottle, free choice protocol. In this paradigm, two drinking bottles were placed into each cage, one containing 0.2% saccharin and the other containing 0.2% saccharin/0.002% cocaine hydrochloride. The position of the bottles was alternated daily. Total fluid intake and cocaine intake were de-

termined daily for 15 days. Voluntary cocaine intake was taken as the total amount of cocaine consumed in a two-bottle, free choice paradigm during the last 5 days. Different groups of rats were used to investigate the effect of acupuncture on voluntary cocaine intake using the same method as described above. Following a 15-day drinking trial, rats were given acupuncture for 1min twice a day with an additional 10-day drinking trial. Basal values of voluntary cocaine intake was defined as the total amount of cocaine consumed during the last five days(days 11 to 15).

### 6. Statistical analysis

Statistical analysis of data was carried out using the SPSS 8.0 and Statview 5.0 software programs. Serial samples of dopamine, DOPAC, HVA values were statistically analyzed by repeated-measures ANOVAs and posthoc Fisher's LSD tests to compare the experimental and control groups. Pearson regression analysis was used to determine if there was a significant relationship between voluntary cocaine intake and increases in extracellular dopamine levels.

## Ⅲ. Results and Conclusion

1. Acupuncture at HT7 but not at a non-specific point(PC6) and at a control point(tail) significantly attenuated the dopamine increase induced by an acute cocaine injection <Fig. 1~ Fig. 3>.

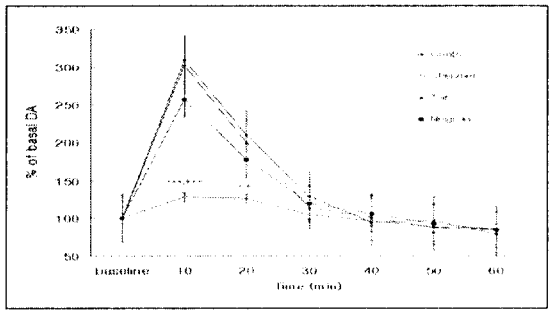


Fig. 1. Effect of acupuncture on changes in extracellular dopamine levels in nucleus accumbens of rats challenged with cocaine.

Male Sprague-Dawley rats received acupuncture for 1min at corresponding to bilateral HT7(Shenmen, n=11) for 1min before an intravenous injection of cocaine hydrochloride(Control, n=7). Acupuncture points corresponding to bilateral PC6(Neiguan, n=11) and tail (Tail, n=7) were used as control points to avoid the direct effect of mechanical stimulation. Results are means±SEM of the amount of DA in each sample expressed as percent of basal values. Data were analyzed by repeated ANOVA and followed by LSD test. $^{*}$, $P<0.05$, $^{***}$, $P<0.001$, as compared with corresponding data of control group. $^{+}$, $P<0.05$, $^{+++}$, $P<0.001$, as compared with corresponding data of tail group.

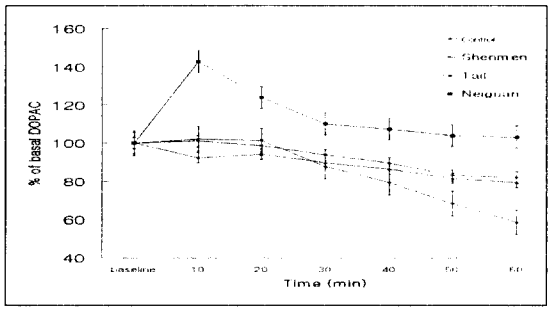


Fig. 2. Effect of acupuncture on changes in extracellular DOPAC levels in nucleus accumbens of rats challenged with cocaine.

Male Sprague-Dawley rats received acupuncture for 1min at corresponding to bilateral HT7(Shenmen, n=11) for 1min before an intravenous injection of cocaine hydrochloride(Control, n=7). Acupuncture points corresponding to bilateral PC6(Neiguan, n=11) and tail (Tail, n=7) were used as control points to avoid the direct effect of mechanical stimulation. Results are means±SEM of the amount of DOPAC in each sample expressed as percent of basal values.

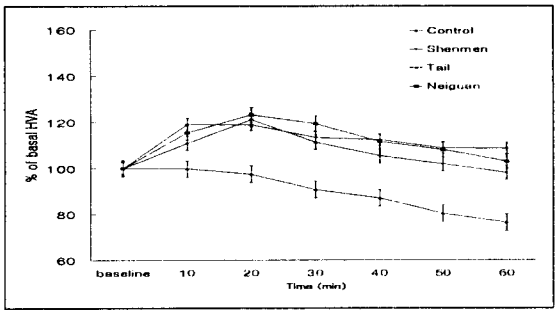


Fig. 3. Effect of acupuncture on changes in extracellular HVA levels in nucleus accumbens of rats challenged with cocaine.

Male Sprague-Dawley rats received acupuncture for 1min at corresponding to bilateral HT7(Shenmen, n=11) for 1min before an intravenous injection of cocaine Hydrochloride(Control, n=7). Acupuncture points corresponding to bilateral PC6(Neiguan, n=11) and tail (Tail, n=7) were used as control points to avoid the direct effect of m stimulation. Results are means±SEM of the amount of HVA in each sample expressed as percent of basal values.

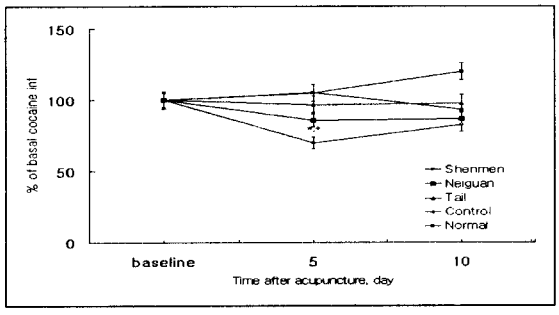


Fig. 4. Effect of acupuncture on voluntary cocaine intake.

Results are means±SEM of the amount of cocaine intake over 5 days after acupuncture in each rat expressed as the percent of basal values. Basal values of voluntary cocaine intake was taken as the total amount of cocaine consumed in a two-bottle, free choice paradigm during the last 5 days(days 11~15) of 15-day drinking trial. n=7~11 for each group. Data were analyzed by repeated ANOVA and followed by LSD test. *, P<0.05 as compared with the corresponding data of control group, +, P<0.05 as compared with the corresponding date of tail group.

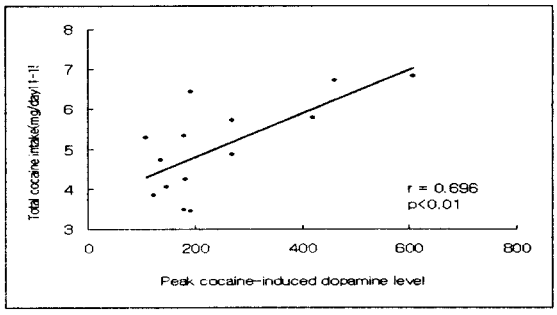


Fig. 5. Graphs show correlation of voluntary cocaine intake(n=14) and increases extracellular dopamine levels in the nucleus accumbens induced by acute cocaine injection of individual rats. Pearson correlation coefficient are shown.

2. Acupuncture at HT7 effectively reduced voluntary cocaine intake in a two-bottle, free choice protocol<Fig. 4>.

3. A significant correlation was found between cocaine-induced increase in extracellular dopamine in the nucleus accumbens and the voluntary intake of cocaine<Fig. 5>.

4. These results suggest that reduction in voluntary cocaine intake by acupuncture are probably mediated via an attenuation of the dopamine increase in the nucleus accumbens induced by an acute cocaine injection.

## Ⅳ. Discussion

The neurobilogical substrate for cocaine self-administration by animals and cocaine in hu-

mans is believed to involve among other biological substrates the mesocortico limbic DA system. This system originates in the ventral midbrain and projects to the nucleus accumbens, and seems to be primarily responsible for the reinforcing effects of cocaine[13)~21)]. Consistent with the pharmacological action of cocaine as a competitive inhibitor of brain catecholamine uptake[22),23)], cocaine has been shown to cause transient but significant elevations of extracellular dopamine levels in the striatum, nucleus accumbens(NAc), and frontal cortex. However the precise relationship between changes in dopamine and specific cocaine-related behaviors remains to be elucidated. All studies measuring extracellular dopamine responses to cocaine showed marked variations among animals and rats self-administer cocaine intravenously at different rates or quantities[24),25)] or voluntarily drink variable, albeit consistent, amounts of cocaine solution according to individual preferences[26)~28)]. Based on these observations, our study utilized individual differences as a means to gain insight into the mechanism mediating self-administration behavior by correlating voluntary drug-intake with dopamine responses to acute cocaine injection.

Anatomical, histochemical, and pharmacological studies of nucleus accumbens(NAc) indicate that this brain area is heterogeneous and can be divided into subregions termed the "shell" and "core"[29)~31)]. Recent evidences suggests that the reinforcing and sensitizing properties of psychostimulants such as cocaine and amphetamine[32)~35)] seem to be differentially regulated in the core region compared to the shell region of the accumbens[33),34)]. Furthermore, the dopamine transporter is more sensitive to cocaine in the shell compared to the core[32)], and psychostimulant drugs increase selectively glucose utilization in this area[35)]. These findings are consistent with the fact that anatomical connections of the shell are related more to limbic structures, whereas those of the core are related more to motor structures[36),37)].

Therefore dopamine responses within the shell are related to cocaine self-administration, suggesting a crucial role of dopamine for this brain area in mediating motivational drug-seeking effects. The present study was designed to investigate acupuncture on acute cocaine-induced changes in extracellular dopamine levels in the nucleus accumbens shell and to measure the effect of acupuncture on voluntary cocaine intake.

Results showed that acupuncture at HT7, but not at a non-specific acupoint point(PC6) or at a control point(tail), significantly attenuated the dopamine release induced by an acute cocaine challenge and effectively reduced voluntary cocaine intake in a two-bottle, free choice protocol. Furthermore, a significant positive correlation was found between cocaine-induced increase in extracellular dopamine in the nucleus accumbens shell and the voluntary intake of cocaine.

In conclusion, our results indicate that reduction in voluntary cocaine intake by acupuncture may be mediated with reduction of dopamine release in the nucleus accumbens shell. In ad-

diction, our results show neurochemical evidence for the biological effects of acupuncture that ultimately may help us to understand how acupuncture can be used to treat cocaine addiction.

【Acknowledgement】

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