

Original Article

A Synergy Effect of Combination of Acupoints in Cocaine Take

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국문초록

코카인 중독에서 경혈의 복합사용에 따른 상승 효과

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목적 : 침술은 한국과 같은 동아시아에서 잘 알려진 효과적인 치료법이며 정신 이상을 포함한 다양한 질

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환의 치료에 사용되어 왔다. 서양에서 침술은 유용한 보완대체의학으로서 각광을 받고 있다. 본 연구는 침술이 코카인 섭취를 줄이는 데에 있어서 효과가 있는지, 또 경혈의 복합 처방이 단일 경혈에 비해 더 효과적인지 여부를 알아보려고 계획되었다.

방법 : 본 실험에서는 270~300 그램의 웅성 흰쥐에게 FR 1 프로그램에서 먹이를 자가 섭취하도록 훈련시켰다. 동물이 3일 연속 3시간 이내에 100개의 먹이를 섭취하면 수술을 하였다. 복강주사로 마취를 시킨 뒤 오른쪽 경정맥으로 관을 삽입하고 천으로 고정시켰다. 회복기를 끝낸 동물은 매일 1시간 동안 FR 3 프로그램으로 코카인을 섭취하도록 훈련 받았다. 3일 연속 섭취량이 일정하면 다음날 한의사가 1분간 침 처치를 하였다. 대조군은 침 자극을 제외하고 똑 같은 조건으로 하였다.

결과 : 신문혈은 코카인 섭취를 줄였으나, 다른 경혈은 그렇지 못하였다. 더구나 신문과 태연을 같이 자침한 경우 단일 경혈에 비해 약간 더 억제하는 효과를 보였다. 그럼에도 불구하고 침술이 식욕에는 별다른 영향을 주지 않았다.

결론 : 이러한 연구 결과는 침술이 적어도 어느 정도 코카인 남용 치료에 있어서 유용하며 경혈을 복합으로 사용하는 것이 단독 사용보다 더 우수할 수 있음을 제시한다.

핵심단어 : 신문, 태연, 조합, 코카인, 자가 투여, 약물 남용, 흰쥐

I. Introduction

Cocaine has been well known as a representative drug of abuse. Frequent exposure to cocaine makes victims dependent¹⁾ and ultimately tends to guide them into addiction. According to many studies, drug abuse is associated with the reinforcing effect and the exhibition of this reinforcing effect is mediated by dopamine(DA) playing an important role in the mesolimbic reward system including ventral tegmental area(VTA) and nucleus accumbens(NAc)²⁻⁶⁾. As well, some studies said that cocaine exhibits its reinforcement maintaining self-administration through the inhibition of DA reuptake in synapse⁷⁻⁹⁾.

In eastern countries such as Korea and China, acupuncture has been used widely for diverse disease including mental disorders and substance abuse, and nowadays, acupuncture is gaining more and more interest as a complementary and alternative medicine in western country^{10,11)}. What was more, NIH accepted that acupuncture might be helpful in the treatment of pain, including drug

addiction¹²⁾. In parallel with this trend, many studies have suggested that acupuncture is useful for the treatment of drug abuse. Ren et al. demonstrated that acupuncture attenuated the expression of conditioned place preference induced by cocaine in rats¹³⁾, and Shi et al. demonstrated that high frequency electroacupuncture inhibited the conditioned place preference caused by morphine¹⁴⁾. Furthermore, acupuncture suppressed c-Fos expression in the NAc and striatum as well as behavioural sensitization induced by repeated nicotine exposure in rats¹⁵⁾. Although more researches are needed to confirm the function and define the exact mechanism, it may be said that acupuncture became a useful method in the treatment of drug abuse.

Among the meridians, heart channel is related with heart disease, circulatory disease, mental disorder, and psychiatric problem, and HT₇ on the heart channel has been especially used for the mental and psychiatric disorders¹⁶⁻¹⁸⁾.

LU₉ of lung channel located on the transverse crease of fore paw like HT₇ is usually used for the modulation of heart function as well as the treatment of the diseases associated with the disorders

of the pulmonary function in human¹⁹⁾. According to Choi et al, it has been demonstrated that SL₄ of greater Yang meridian attenuated locomotor activity of rats sensitized to methamphetamine²⁰⁾, and Lee et al. said that greater Yang meridian accompanies with greater Yin meridian in six-meridian theory²¹⁾. Based on these, LU₉ which is a source point of greater Yin meridian²²⁾ was thought to be effective on cocaine sensitized-behavior.

In the previous study, some researchers have demonstrated that acupuncture at HT₇ modulated DA level in the nucleus accumbens(NAc) in alcohol sensitization and withdrawal through gamma amino-butyric acid(GABA) receptor system^{23,24)}. In addition, acupuncture at HT₇ ameliorated the locomotor activity and c-Fos gene expression in morphine sensitized rats²⁵⁾. Furthermore, acupuncture at HT₇ has shown that locomotor activity and tyrosine hydroxylase expression were able to be modulated by acupuncture in cocaine sensitized rats²⁶⁾. Thus, acupuncture at HT₇ has been shown to be effective in the normalization of the neurochemical changes and behavioral disorders induced by drug abuse.

Based on these results, the possibility whether acupuncture at HT₇ could affect cocaine intake or not was examined using self-administration fixed ratio(FR) 3 schedule.

II. Materials and methods

1. Animals

Male Sprague-Dawley rats(Daehan Animal, Seoul, Korea) were used and their weights were 270~300g at the beginning of the experiment. Rats were allowed free access to the food and water and maintained on a 12h light-dark cycle, except that animals were kept under overnight schedule on the 1st day of the food training. Measures were performed in the minimization of stress in accordance with NIH Guidelines for the Care and Use of Laboratory Animals(NIH publication no. 80-23).

2. Apparatus

Self-administration of cocaine and food was carried out in the same operant chambers covered with sound-attenuated wood cubicles(Med Associates, St. Albans, VT). Chambers have two kinds of lights i.e. the house lights on a wall, and cue lights above the active lever on the opposite wall. The signal of active lever-press was delivered to computer operating schedule manager program and the motor equipped with the syringe of cocaine solution worked according to experiment design.

3. Food training

Animals that have passed 3 days of the adaptation period to the home cage and experimental environment were subjected for the experiments. Animals were trained to press the active lever for 45mg sucrose pellets under a daily fixed ratio(FR) 1 schedule. Rats were required to achieve 100 sucrose pellets within 3h with exception of the first day on which animals tried throughout night without limitation of time. The house light was extinguished and cue light was illuminated across the food training. Food training was performed once a day under food restriction to facilitate the learning of active lever-press. When animal had succeeded in achieving 100 sucrose pellets for 3 consecutive days, they were passed to the next phase of surgery.

4. Surgery

Animals that had underwent the food training (100 sucrose pellets within 3h for three consecutive tests) freely took the food and water for at least 1 day. Then, anesthetization with sodium pentobarbital(50mg/kg, i.p.) injection was conducted. Chronic silastic jugular vein catheters(0.02 "ID × 0.037" OD) coated with tridodecylmethyl ammonium chloride (TDMAC) heparin(Polysciences Inc, Warrington, PA) were surgically implanted and fixed with mersilene surgical mesh(Ethicon Inc). The catheters were

exteriorized in the back of animals through 22 gauge guide cannulae (Palstics One, Roanoke, VA, USA) after skin incision. Silastic tubing and guide cannulae were embedded in dental cement and secured with Prolene surgical mesh. The patency of the catheters during recovery period was maintained by daily infusion of 0.2ml of saline containing heparin.

5. Cocaine training

Animals were trained to self-administer cocaine hydrochloride dissolved in saline after recovery period of at least 10 days, and 0.2ml of heparin was infused into the guide cannula of jugular vein before and after the session to maintain the patency of the catheters. When animals press the active lever, 0.1ml of cocaine hydrochloride solution was delivered through intravenous catheters for 5sec with the simultaneous extinguishment of the house light and the illumination of cue light. After 5 sec of cocaine injection, the "time-out"(TO) period of 10 sec was occurred in which both of house light and cue light were extinguished and no result was produced. After TO period, the house light was illuminated again. The responses of inactive lever were recorded however produced no result. Initially, animals were trained to self-administer 1.0mg/kg of cocaine to promote the cocaine intake in daily 4h session of FR 1 schedule for 3 days. Then, cocaine dose was decreased to 0.25mg/kg on the 4th day. Animals that had taken 0.25mg/kg of cocaine constantly faced the reduction of session time to 1h. When rats succeeded in taking the cocaine solution stably with 1h session under FR 1 schedule, the responses of active lever were checked and animals who had established the stable baseline (variation of active lever responses for 3 consecutive sessions less than 10% of the mean) were passed to the next phase of FR 3 schedule in which 3 presses of active lever were needed for the infusion of cocaine.

6. Test and acupuncture treatment

Animals that had established the baseline of infusion under FR 3 schedule were given acupuncture on the next day of baseline. Each treatment was performed randomly without special order after each establishment of baseline, and each animal received all of treatments. Animals of HT₇ group (*n*=5) were given acupuncture at bilateral HT₇ points of heart channel, PC₆ group (*n*=5) at PC₆ points of pericardium channel, and LU₉ group (*n*=5) at LU₉ points of lung channel. Rats of HT₇+LU₉ group (*n*=5) received acupuncture at bilateral HT₇ and LU₉ simultaneously. Rats of tail group (*n*=5) received acupuncture at tail points to determine whether the mechanical stimulation at non-acupoints influences on cocaine taking behavior or not. Rats of control group (*n*=5) received the same treatment with acupuncture group except needle insertion.

For the tail points, needles were inserted into nonacupoints apart one fifth of tail length from the proximal region of the tail to avoid the two tail acupoints (proximal tail and tip of the tail). These nonacupoints are distal to the proximal tail acupoints. The anatomical locations of stimulated acupoints in rats were determined in accordance with other's^{27,28)}.

For the acupuncture treatment, stainless-steel needles used in this study has a diameter of 0.18mm and a length of 8mm, and inserted vertically into a depth of 2~3mm on each points for 1 min. The same oriental medical doctor who has major in meridian and acupoint performed all acupuncture treatment. The acupuncture stimulation was delivered manually by twisting needles at a frequency of twice per sec for a total of 2 sec of stimulation while needles were inserted and withdrawn from acupoints. Animals received a slight restriction of movement for 1 min of acupuncture treatment by the other researcher and handling was given before for 2 min to minimize the stress following restriction.

7. Food latency

Other animals were trained to take food pellets for the experiment of the examination about the effect of acupuncture on food taking. Rats were trained to press the active lever for sucrose pellets under daily FR 1 schedule receiving food restriction similarly with food training and required to achieve 100 pellets within 5 min. Animals that had succeeded during 3 consecutive days, were passed to the next phase of FR 3 schedule in which 3 presses of active lever were needed for the achievement of the food pellet. The time(sec) spent for 100 pellets was checked, and rats that had shown the establishment of baseline (variation of time spent for 100 pellets for 3 consecutive sessions less than 20% of the mean) were subject for each treatment on the next day of baseline. Acupuncture group ($n=7$) received acupuncture stimulation on bilateral HT₇, and control group ($n=6$) were given the same treatment with acupuncture group without needle stimulation. Responses of inactive lever were recorded with no consequence. The time for 100 pellets was checked and compared with baseline.

8. Statistical analysis

Schedule manager program (Med Associates, St. Albans, VT) collected the data, and the statistical analysis was carried out with one-way analysis of variance (ANOVA) and post hoc the least significant difference (LSD) test using SPSS statistics program. The statistical significance was accepted with the P value less than 0.05.

III. Results

1. The basal level of infusion of cocaine solution

All treatments were done randomly and the results of present study show that the basal level

of active lever response was 31.86 ± 5.44 for control group, 29.80 ± 4.86 for HT₇ group, 30.12 ± 3.03 for PC₆ group, 32.28 ± 4.41 for tail group, 30.54 ± 2.74 for LU₉ group, and 34.28 ± 3.49 for HT₇+LU₉ group. From this result, it has been demonstrated that the basal levels of active lever-presses for 3 days before treatments were very similar in all treatment. Even if the basal level of HT₇ group was lower and that of HT₇+LU₉ group was higher a little, however there was no significant difference between groups (Fig. 1).

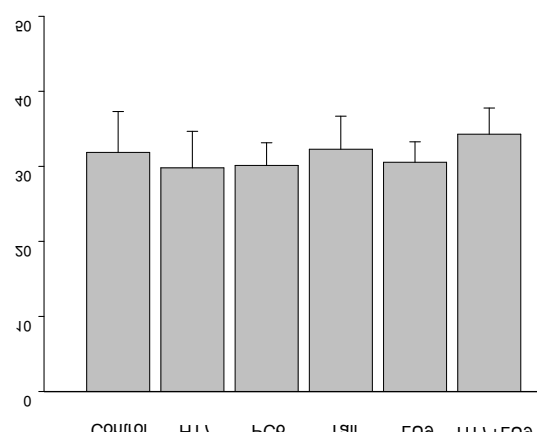


Fig. 1. The basal level of infusion of cocaine solution. Results are mean \pm S.E.M. of infusions.

One way ANOVA and post hoc LSD test. Each group $n=5$. Control : animals that received the same treatment with acupuncture group except needle stimulation ; HT₇ : animals that received acupuncture at HT₇ ; PC₆ : animals that received acupuncture at PC₆ ; Tail : animals that received acupuncture at nonacupoint in tail ; LU₉ : animals that received acupuncture at LU₉ ; HT₇+LU₉ : animals that received acupuncture simultaneously at HT₇ and LU₉.

2. The effect of acupuncture on the active lever response

The results of present study show that the active lever response was 103.80 ± 12.82 for control group, 79.80 ± 16.34 for HT₇ group, 93.20 ± 13.11 for PC₆ group, 89.40 ± 14.86 for tail group, 86.40 ± 8.40 for LU₉ group, and 81.60 ± 10.71 for HT₇+LU₉ group. So, it was demonstrated that acupuncture at HT₇ reduced cocaine intake to 76.9% of control, and acupuncture at HT₇+LU₉ reduced to 78.6% of control, and the representative pattern of cocaine taking behavior in each group was presented using hatch mark (Fig. 2).

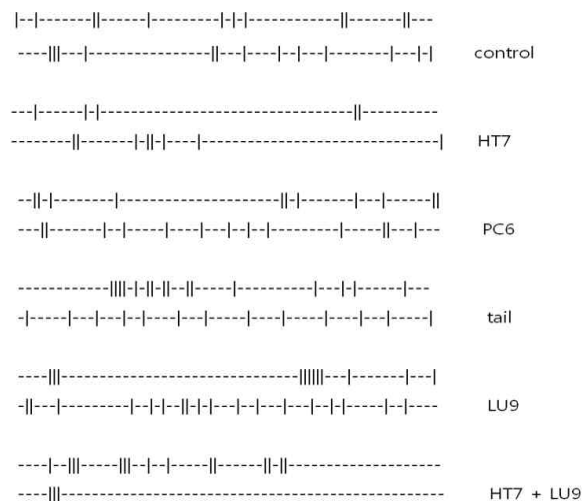


Fig. 2. The representative hatch marks of active lever presses during 2h session time in each group
A hatch means the moment at which animal acquired cocaine by pressing active lever.

3. The effect of acupuncture on the inactive lever response

The results of present study show that the inactive lever response was 0.00±0.00 for control group, 0.00±0.00 for HT₇ group, 0.00±0.00 for PC₆ group, 0.00±0.00 for tail group, 0.00±0.00 for LU₉ group, and 0.20±0.45 for HT₇+LU₉ group. There was no significant difference between 6 groups. So,

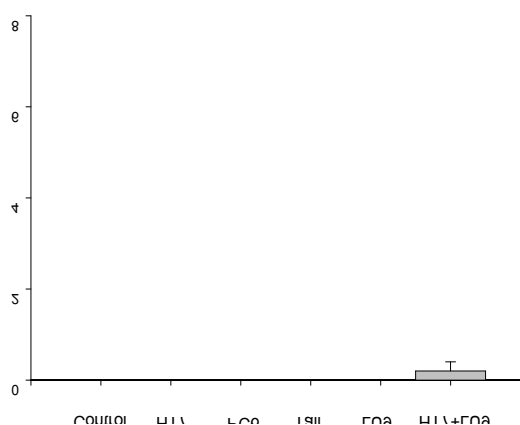


Fig. 3. The effect of acupuncture on the inactive lever response

Results are mean±S.E.M. of responses.
One-way ANOVA and post hoc LSD test. Each group *n*=5. 0.00±0.00 for control group ; 0.00±0.00 for HT₇ group ; 0.00±0.00 for PC₆ group ; 0.00±0.00 for tail group ; 0.00±0.00 for LU₉ group ; and 0.20±0.45 for HT₇+LU₉ group.

it has been demonstrated that each treatments had little effect on inactive lever response(Fig. 3).

4. The effect of acupuncture on cocaine taking behavior

The results of present study show that the percent of infusion compared to basal level was 111.68±4.71% for control group, 87.54±8.56% for HT₇ group, 101.18±6.01% for PC₆ group, 91.32±8.31% for tail group, 94.06±1.92% for LU₉ group, and 80.02±7.93% for HT₇+LU₉ group. It has been shown that there are significant differences; HT₇ group vs. control group(*p*<0.05), HT₇+LU₉ group vs. control group(*p*<0.01, Fig. 4).

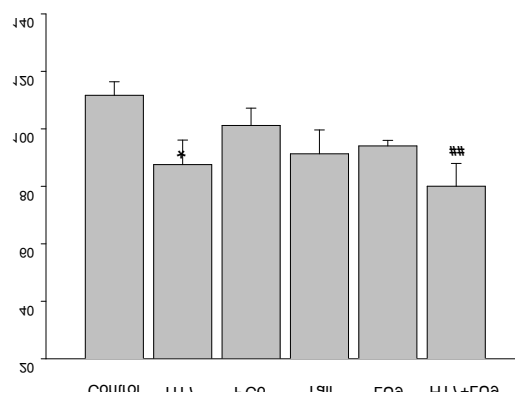


Fig. 4. The effect of acupuncture on cocaine taking behavior

Results are mean±S.E.M. of percents compared to basal level. One-way ANOVA and post hoc LSD test.

* *p*<0.05, HT₇ group vs. control group.

p<0.01, HT₇+LU₉ group vs. control group. Each group *n*=5.

5. The analysis of the effect of acupuncture on cocaine intake using the time course

According to the analysis of infusion of cocaine solution using time course of 5 min interval, it has been shown that there are some significant differences ; HT₇ group vs. control group with 0.33±0.33 vs. 3.00±1.05 at 15 min(*p*<0.05), and HT₇ group vs. tail group with 0.33±0.33 vs. 3.25±0.63 at 15 min(*p*<0.05, Fig. 5).

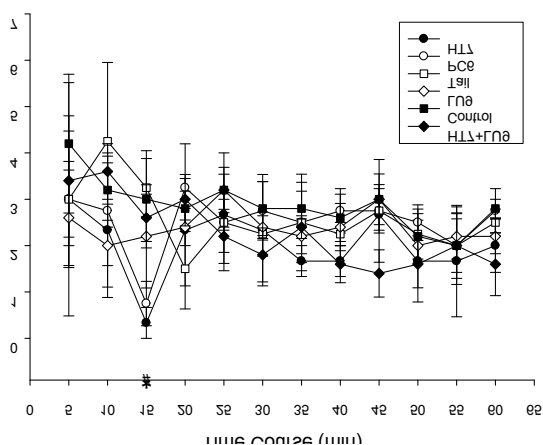


Fig. 5. The analysis of the effect of acupuncture on cocaine intake using the time course

Results are mean±S.E.M. of infusions. One-way ANOVA and post hoc LSD test.

* : $p < 0.05$, HT₇ group vs. control group.

: $p < 0.05$, HT₇ group vs. tail group. Each group $n=5$.

6. The effect of order of treatment on cocaine intake

In this study, each treatment was conducted randomly, and the results of present study show that the mean of the percent compared to basal level in infusion was 105.54±6.92% for the 1st treatment, 96.28±9.74% for the 2nd treatment, 90.98±9.61% for the 3rd treatment, 98.92±5.09% for the 4th treatment, 89.84±4.61% for the 5th treatment, and 84.24±8.13% for the 6th treatment. So, it seems that

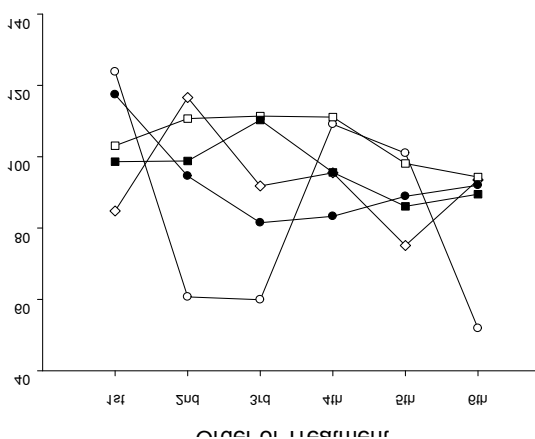


Fig. 6. The effect of order of treatment on cocaine intake

Results are mean±S.E.M. of percents compared to basal level. One-way ANOVA and post hoc LSD test. Each group $n=5$.

there is no relation between the order of treatment and the effect of treatment(Fig. 6).

7. The effect of acupuncture on food intake

The results of present study show that the time spent for 100 sucrose pellets under FR 3 schedule was 779.67±159.32 min for control group and 793.86±135.83 min for HT₇ group. The basal level was 899.55±110.70 min for control group and 958.36±149.00 min for HT₇ group. In both of control group and HT₇ group, treatments shorten rather than

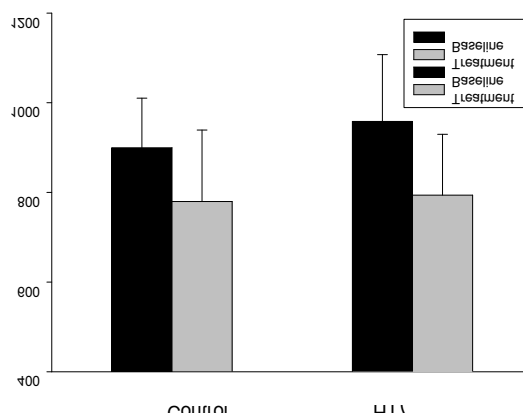


Fig. 7. The effect of acupuncture on food intake (time)

Results are mean±S.E.M. of time(sec) for 100 pellets. One-way ANOVA and post hoc LSD test. Control group $n=6$, HT₇ group $n=7$.

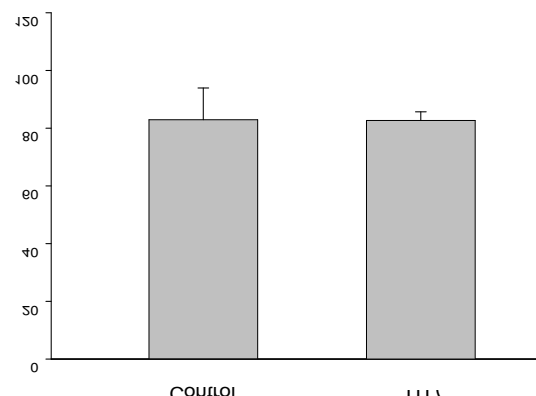


Fig. 8. The effect of acupuncture on food intake (percent)

Results are mean±S.E.M. of percents compared to basal level. One-way ANOVA and post hoc LSD test. Control group $n=6$, HT₇ group $n=7$.

lengthen the time spent for the food taking, and there was no significant difference(Fig. 7).

Conversion of time spent into percent compared to basal level showed that the percent was $82.92 \pm 11.01\%$ for control group and $82.66 \pm 3.02\%$ for HT₇ group. So, it has been demonstrated that there was no significant difference between the effects of two treatments on food taking(Fig. 8).

IV. Discussion

It is well known that cocaine has been severely abused owing to its strong reinforcing effect and tends to eventually drive toward addiction. Many studies have demonstrated that mesolimbic DA system plays an important role in the reinforcing effect of cocaine and its driving tendency into abuse²⁻⁶⁾. As well, the depletion of DA in the mesolimbic system is believed to be responsible for the behavioral withdrawal signs²⁹⁾. Interestingly, some animal studies have suggested that acupuncture at the specific acupoint HT₇ modulated the extracellular DA level in the NAc of mesolimbic system in ethanol sensitized rats, as well as ameliorated the behavioral withdrawal signs in ethanol withdrawn rats^{23,24,30)}. In addition, it has been demonstrated that the behavioral hyperactivity and extracellular DA level of morphine sensitized rats were changed by acupuncture at HT₇. Also, acupuncture has been suggested to be effective in the suppression of cocaine sensitized-behavior by Lee et al.²⁶⁾. The result of the study has shown that the large increase of locomotor activity and tyrosine hydroxylase expression in the ventral tegmental area of mesolimbic DA system were suppressed by HT₇. Based on these results, it was investigated whether acupuncture at HT₇ could affect the cocaine taking behavior or not using self-administration.

Animals subjected for the surgery of the implantation of intravenous catheter into jugular vein were trained to self-administer cocaine solution. As shown in fig. 1, the basal levels of active lever-

presses collected from the data for 3 consecutive days before treatments suggest that animals had taken stably the cocaine solution. Although a little high or low appears, however there was no significant difference between groups and animals of each group had taken similar amount of cocaine stably in daily session time.

However, the animals given acupuncture have shown that the cocaine intake could be reduced by acupuncture. Acupuncture at HT₇ attenuated cocaine intake to $87.54 \pm 8.56\%$ of basal level, and HT₇+LU₉ reduced to $80.02 \pm 7.93\%$. One-way ANOVA followed by post hoc LSD test revealed that this mild suppression is significantly different with other treatment(Fig. 6). Results show that this decrease was caused by attenuation of active lever response. However, the inactive lever press was not affected by acupuncture treatments. So, it may be suggested that the reduction of active lever press was caused by the decrease of spontaneous will of animals to take cocaine, and it may be said that acupuncture made animals be patient.

It is interesting that according to the analysis of the result of this study using time course of 5 min, the effect of HT₇ to reduce cocaine taking appeared at 15 min. The representative pattern of cocaine intake in each group is saying the fact using hatch mark that HT₇ was effective in the first half period.

HT₇ has shown a mild attenuation of the cocaine intake in other study using FR 1 schedule. In the FR 3 schedule, animals need to press the active lever 3 times for an infusion. So, the idea that if it is needed to press 3 times more, animals might give up easy cocaine seeking under the help of acupuncture drove into this design. However, HT₇ showed similar effect in the FR3 schedule. Therefore, it seems to be difficult to say that acupuncture at HT₇ is sufficient to suppress certainly the intake of cocaine.

Lee et al. said that greater yang meridian ac-companies with greater Yin meridian in six-meridian theory, and Choi et al. have demonstrated that SL₄ of greater Yang meridian suppressed hyperactivity of rats sensitized to methamphetamine. So, LU₉

which is located on the wrist of the fore paw like HT₇ and is a source point of greater Yin meridian was recommended to be effective on cocaine sensitized behavior. However, the result has shown that LU₉ had no effect on cocaine taking by itself. Instead, Even if there was no significance between HT₇ group and HT₇+LU₉ group, LU₉ produced a synergy effect with HT₇ together lowering cocaine taking to about 80%. So, it is likely that there is a slight synergy in the effect of acupuncture treatment.

In this study, animals received all of treatments unintentionally with counter balance. This random treatment was performed in order to be free from the possibility that there perhaps is a relation between the order and the effect. However, the result showed that the effects of treatments did not exhibit a tendency to increase or decrease one way in association with the order. So, it seems that there is no relation between the order and the effect in the treatment of this study.

Unfortunately, we know there is a problem needed to be thought seriously in the therapy for drug abuse. According to Weerts and colleagues, it is a severe problem that drugs treating cocaine addiction through GABAergic modulation such as baclofen, CGP44532, and tiagabine, makes side effect like the reduction of food taking³¹. So, a therapy developed to care addiction needs to prove to be safe from these side effects. As described above, it has been shown that acupuncture at HT₇ lowered cocaine taking behavior. Nevertheless, acupuncture did not influence food taking behavior. Acupuncture has shortened rather than lengthen the time spent for 100 pellets to about 82% of basal level like control group as shown in fig. 10. Based on this result, it seems that the effect of suppression by acupuncture is specific for cocaine, and there is little possibility for acupuncture to make a side effect of reduction of food taking.

Taken together, it might be suggested from the results of present study that acupuncture at HT₇ could be considered as an assistant in the attenuation of cocaine intake. Also, it is needed on the

next step to investigate the mechanism in which acupuncture works.

V. Conclusion

According to the results of this study, it has been demonstrated that cocaine taking behavior was reduced significantly in HT₇ group and HT₇+LU₉ group. Also, there was a slight synergy in HT₇+LU₉. The effect of acupuncture was shown in the first half period, and it has been also demonstrated that the effect of acupuncture to reduce active lever was specific for cocaine, and food intake was not affected. As a conclusion, it may be suggested that acupuncture could be useful as an assistant in the treatment of cocaine abuse.

VI. References

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