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# Modafinil in Comparison with DSP4 in Altering Tail Pinch-induced Sensorimotor Gating Effects in Rats

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**Background:** Pre-pulse inhibition of acoustic startle is thought to reflect sensorimotor gating effects, which has proven to be a useful model system for studying effects of psychostimulant drugs in psychopharmacology. A variety of drugs or stressors have been reported to modulate the sensorimotor gating reactivity by altering brain catecholamine neuron activities. Modafinil is a drug increasingly used as a medication for elevating arousal and vigilance, yet its underlying mechanisms are still not fully understood. The purpose of the present study was to determine whether or not brain catecholamine neurons are involved in modafinil's effects on sensorimotor gating reactivity. **Methods:** Rats were divided into three groups, i.e. the pretreatment with modafinil (64 mg/kg, i.p.) group, the selective lesion of the brain dorsal noradrenergic bundle with neurotoxin DSP4 (50 mg/kg, i.p.) group, and the saline control group. A further experiment was performed to verify whether or not the effect of modafinil is counteracted by an effective dose of haloperidol (0.1 mg/kg, s.c.). All rats were measured by PPI of the acoustic startle, including a session in which subjects were exposed to tail-pinch (TP) and the sessions before or after TP. **Results:** The results showed that rats of both the modafinil and DSP4 pretreated groups exhibited the same pattern of effects in enhancing TP-induced PPI disruption. However, a difference was also observed. The induced reduction in PPI was accompanied with a significant elevation of the startle magnitude in the DSP4 group but not in modafinil pretreated group. In addition, further experiment results indicated that a dopamine D2 antagonist, haloperidol, significantly normalized the modafinil-induced PPI disruptive effects. **Conclusion:** These findings suggest that modafinil might precipitate sensorimotor gating deficits in rats confronted by TP stress, similar to the DSP4 pretreated group rats. In respect to these two catecholamine substrates, dopamine and norepinephrine, the PPI effects of modafinil on dopaminergic neurons are substantiated the present study. On the other hand, more experiments are needed to confirm the related mechanisms of noradrenergic neurons in the effects of modafinil.

Key words: pre-pulse inhibition, modafinil, dopamine, norepinephrine, tail pinch

## INTRODUCTION

Sensorimotor gating was examined by measuring the prepulse inhibition of the startle reflex. This test has been used in animals as well as in humans. Subjects reaction to a sudden loud acoustic stimulus elicit strong muscle contractions (startle magnitude); however, when the stimulus is preceded by a soft pre-pulse, the severity of this reaction is inhibited, i.e. pre-pulse inhibition (PPI).[1] Clinically, PPI is used as a marker for sensory and cognitive information-processing mechanisms, which could be lacking in a number of neuropsychiatric disorders.[2] Sensitivity to stress is known to be linked to a variety of physical and psychological disorders. Stress may also be a confounding factor in PPI[3-4] and startle[5] responsiveness. Several animal models for stress have been used to investigate new anti-psychotics,[3] while the common rodent model of mild physical stress by pinching of the tail, tail pinch (TP),[6] was used in the present study.

A number of brain regions containing neurotransmitter substrates have been found to take part in control of sensorimotor gating (PPI) regulations.[1,7-8] Of these, PPI is regulated by catecholamines including norepinephrine (NE) and dopamine (DA). These two catecholamines are neurochemically separable but the midbrain DA trans-

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mission appears prominent. Most psychostimulant drugs with effects on midbrain DA neurons have been reported to produce PPI disruptions, but there have only been a few reports indicating the participation of NE neurons on those effects.[1,7-8] However, depletion of NE transmission by the selective neurotoxin N-(2-chloroethyl-N-ethyl-2-bromobenzylamine) (DSP4) has been reported to prevent both PCP and amphetamine-induced PPI disruptions.[9-10] In addition, pretreatment of rats with phenoxybenzamine, an adrenergic receptor antagonist, has been reported to attenuate the effects of p,p'-DDT on the acoustic startle reflex.[11] The evidence mentioned above indicates that brain NE transmission is important and that its role in sensorimotor gating mechanisms must be elucidated.

Stress may lead to brain pathophysiological changes by activation of two noradrenergic pathways,[12] pathways that originate from two distinct groups of neurons in the brainstem, i.e. the locus coeruleus and the lateral tegmentum.[13] The nucleus locus coeruleus sends an ascending bundle that innervates the majority of noradrenergic terminal areas, such as the prefrontal cortex, hippocampus, amygdale, cerebellum, and spinal cord. This projection is commonly referred to as the dorsal noradrenergic bundle (DNEB). On the other hand, efferent projections from the lateral tegmentum build up the ventral noradrenergic bundle (VNEB), which has less extensive projections compared to the DNEB and mainly innervates the hypothalamus, pre-optic area, bed nucleus of the stria terminalis, and certain other sub-cortical limbic regions. The DNEB pathway is crucial in regulation of organisms' overall state of arousal and attention,[14] but the functional role of VNEB pathway is still unclear. Since VNEB projects mostly to the basal forebrain areas, we suppose that VNEB might counterbalance with DNEB to maintain animal behaviors, particularly the emotional behaviors, in homeostasis.

Modafinil (2-[(diphenylmethyl)sulfinyl]acetamide), a novel wake-promoting agent that has received U.S. Food and Drug Administration (FDA) approval for treatment of daytime sleepiness in narcolepsy, is suggested to be more potent than caffeine and to present less potential for addiction compared with classical psychostimulant drugs, such as cocaine and amphetamines.[5,15] Despite the expanding clinical indications of this drug, the precise mechanism is still unknown. It has been hypothesized that the effects on both NE[16-19] and DA[20-22] neurotransmitter substrates mediate the wake-promoting effects of this compound. Recently, specific concerns have emerged that modafinil might produce psychoactive and euphoric effects similar to those of classical psychstimulant drugs.[23-26] In addition, the effects of modafinil on brain areas, where by reciprocal neural circuits linking prefrontal cortexes, amygdale, and hypothalamus are known areas innervated by VNEB neurons, are also areas known to be important in animal stress and emotion control mechanisms.[27-28]

It has been made evident that TP-induced mild stress of rats may activate their brain catecholamine transmissions by enhancing NE-DA interactions.[29] In the present study, we compared the effects of modafinil versus selective lesions of DNEB neurons to signify the importance of specific brain NE transmissions in PPI regulations. Selective targeting of DNEB projections is made practical by using of the neurotoxin agent DSP4, which when systemically co-administrated with zimeldine has been proved to lesion DNEB with good selectivity.[30-31] The effects were monitored with the quantitative measures of the startle magnitude and PPI, together with TP-induced mild stress in rats.

## MATERIALS AND METHODS

### Animals

Male adult Sprague–Dawley rats weighing between 250 and 300 g were supplied by BioLASCO Taiwan Co., Ltd. The animals were housed in groups of three at a constant cage temperature ($22\pm1^{o}$C) and humidity (40-70%). The animals were allowed to adapt for 1 week to the novel environment before any experiment was performed. They were kept under regular light–dark conditions (light on at 07:00 a.m. and off at 19:00 p.m.) with food and water available ad libitum except during behavioral testing. There were 5-8 rats per treatment group. The Institutional Animal Care and Use Committee in National Defense Medical Center approved this study.

### Apparatus

Each of the four startle chambers (SR-LAB, San Diego Instrument, San Diego, CA) were housed in a sound-attenuated room with a 60 dB ambient noise level. The chambers consisted of a Plexiglas cylinder 8.2 cm in diameter resting on a $12.5\times25.5$ cm Plexiglas frame within a ventilated enclosure. Acoustic noise bursts were presented via a speaker mounted 24 cm above the animal. A piezoelectric accelerometer mounted below the Plexiglas frame detected and transported motion within the cylinder. The delivery of acoustic stimuli were controlled by the SR-LAB microcomputer and interface assembly which also digitized (0-4095), rectified and

recorded stabilimeter reading, with one hundred 1-ms readings collected beginning at stimulus onset. Startle amplitudes were defined as the average of 100 readings. Background noise and all acoustic stimuli were delivered through one Radio Shack Supertweeter (frequency response predominantly between 5 and 16 KHz) in each chamber. Stimulus intensities and response sensitivities were calibrated to be nearly identical in each of the four startle chambers (maximum variability < 1% of stimulus range and < 5% of response ranges), and chambers were also balanced across all experiment groups. Sound levels were calibrated by a Quest Sound Level Meter to make them relative to a 20 uN/M2 scale. The microphone was placed inside the Plexiglas cylinder. Response sensitivities were calibrated using an SR-LAB Startle Calibration System.

**Testing Procedure**

The study was expressed in four experiments. The rats were randomly assigned to the experimental groups in such a way that each rat did not differ significantly in weight at the beginning of the experiment. The first three experimental groups, i.e. vehicle (saline) control (n=8) versus neurotoxin DSP4 (n=7) or modafinil (64 mg/kg, n=7) pretreatment groups, were carried out to verify whether or not modafinil possesses an effect on startle and PPI responses during TP stress and to what degree the brain NE system was involved. The fourth experiment was designed to assess the ability of DA D2 antagonist to reverse the effect induced by modafinil. In this experiment, a total of 19 rats were administered with either haloperidol (0.1 mg/kg) plus modafinil (64 mg/kg) (n=7), vehicle plus modafinil (64 mg/kg) (n=7), or haloperidol (0.1 mg/kg) plus vehicle (n=5). The same TP stress procedure was followed for all experiments, i.e. all rats were measured by the pre-pulse inhibition of the acoustic startle in the three test sessions, while the second test session (TP) was exposed to TP stressor, but the first (before tail-pinch, pre-TP) and third (after tail-pinch, post-TP) ones were not. In general, an average of 2 mins separated the consecutive sessions.

The PPI of the acoustic startle was measured by exposing the rats to a series of acoustic pulses with or without a short acoustic pre-pulse. The pulses caused muscle contractions in the bodies of the rats through an involuntary reflex, which was measured as startle amplitude. If a pre-pulse just above background noise (70 dB) preceded a pulse the reaction to the pulse was inhibited. Rats were placed in the cylinder and the test session started with a habituation period of 5 min, followed by a block of trials of acoustic pulses without a pre-pulse to investigate the basic acoustic startle. The test session utilized in all of the experiments contained five different trial types and had a total duration of 20 min: a pulse-alone trial in which a 40-msec, 118-dB broadband burst was presented. Three trials of prepulse-pulse pairs in which 20-msec noises that were 3, 5 or 10 dB above the background noise were presented 80 msec before the onset of the 118-dB pulse. Finally, a no stimulus trial, which included only the background noise, was presented. An average of 15 sec (ranging from 9 to 21 sec) separated consecutive trials. The startle response was measured during 100 ms (1/ms) from the start of the pulse. The startle amplitude was defined as the mean of the 100 measurements. The percentage of inhibition of the acoustic startle due to the pre-pulse was calculated per pre-pulse intensity.

**The Tail-pinch Stressor**

Prior to injection, the tails of rats were marked with a felt tipped marker at a diameter of 4.3 mm. These measurements were made using standard metal calipers. The tails were re-measured and remarked prior to each TP session to control for possible differences in diameter due to edema or growth of the animals. Rats were placed in the center of the startle test chamber, the length of the tail was guided through the chamber's floor, and a cotton-padded clip was applied at the previously marked diameter to avoid tail damage. Rats did not vocalize during application of TP pressure. Animals were observed for a period of four minutes. After observation, the forceps were removed and the animals were returned immediately to their cages.

**Dorsal Noradrenergic Bundle Lesions**

Rats were given an intraperitoneal injection of DSP-4 (50 mg/kg) 7 days prior to the start of the behavioral testing.[30] All rats were pretreated with the selective serotonin reuptake inhibitor zimeldine (10 mg/kg, i.p.) 30 min prior to DSP4 administration, in order to protect serotonergic nerve terminals.[31] The rats were handled daily following the lesion.

**Drugs**

All drugs were freshly prepared prior to use. Modafinil was supplied from Dr. A.R. Lee's laboratory at the National Defense Medical Center. The drug was suspended in a 0.5% gum Arabic solution and administered intraperitoneally (i.p). Zimeldine (Sigma, USA) was dissolved in distilled water and sonicated mildly. DSP-4 (Sigma, USA) was dissolved in 0.9% saline. The above two drugs

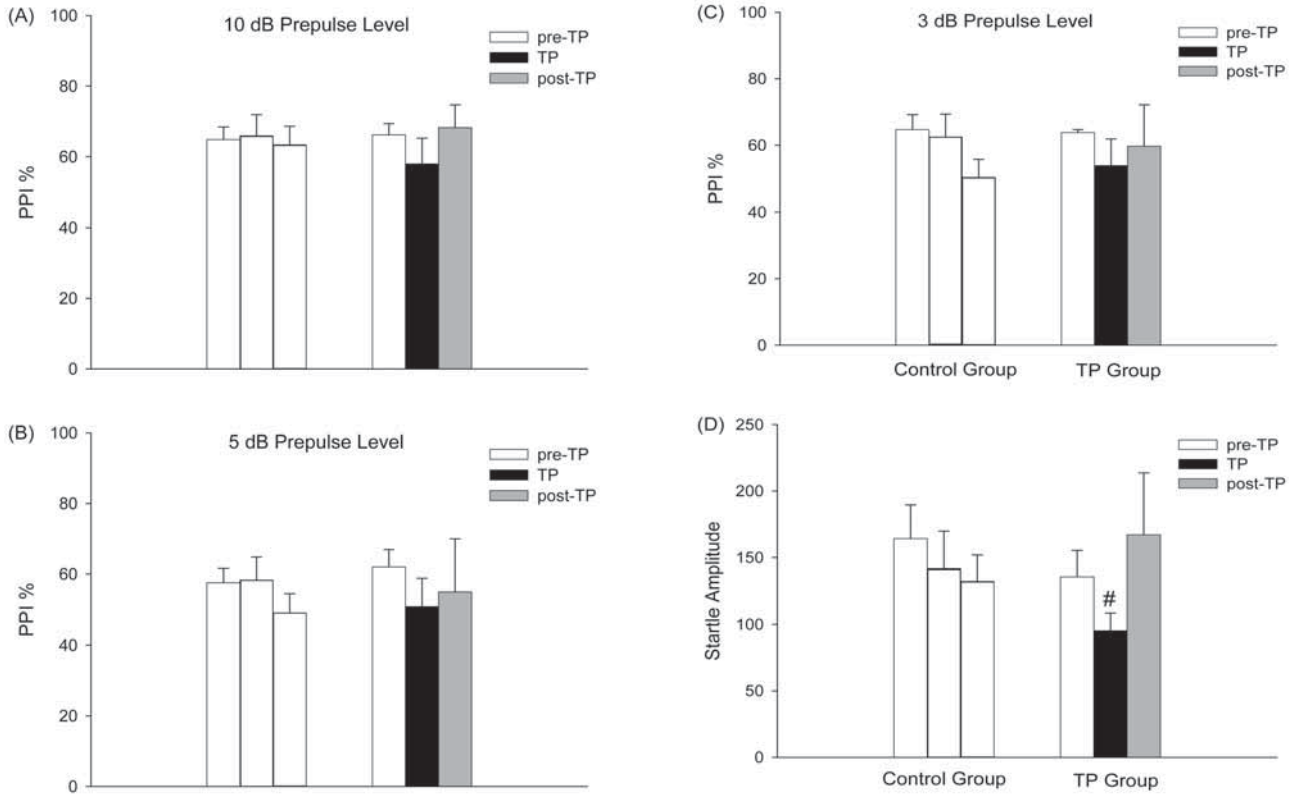


Fig. 1 Effect of tail pinch on PPI of acoustic startle in rats. The rats were separated into two groups, with tail-pinch stressor (TP Group) and without (Control Group). In rats confronted by this stressor, while TP was exposed to the tail-pinch, pre-TP was the stage before tail-pinch, and post-TP was the stage after tail-pinch. An average of 2 min separated consecutive sessions. (a, b, c) PPI (%) at three different prepulse intensities (80, 75, and 73 dB). (d) Acoustic startle amplitude was measured in trials without a prepulse. Repeated one-way ANOVA showed a significant effect of tail-pinch on startle amplitude (F=6.968, p=0.039). A post hoc comparison of the group mean by a Tukey test indicated statistical significance (#) between TP and pre-TP stage. Values indicate the mean±SE. # p<0.05.

were administered intraperitoneally as week. Haloperidol (Sigma, USA) was dissolved in a 10% lactic acid solution while the pH was adjusted to 7 with a NaOH solution, and administered subcutaneously.

**Data Analysis**

The PPI value was calculated with the following formula: [1-(startle amplitude following prepulse + pulse pair / startle amplitude following pulse-alone)] X 100%. Data were analyzed using the SPSS 12.0 statistical package. For the percentages of PPI data and startle amplitude, data from each measurement were analyzed with a repeated one-way ANOVA followed by Tukey tests to detect differences between pairs of sessions. An Independent T-test was conducted to determine the group differences at the indicated session points. The criterion for statistical significance was taken to be p<0.05.

## RESULTS

**Effect of TP Stress on PPI of Acoustic Startle**

Effects of TP on startle responses and PPI in vehicle control rats are shown in Figure 1. In general, no differences were observed in the percentages of PPI responses following prepulse (73, 75, 80 dBs)+pulse (118-dB) pairs between naive (Control Group) and TP stressor (TP Group) (left panel) rats. As for startle amplitudes of pulse alone (right panel), TP stress had a significant effect when compared with the pre-TP session without tail pinch. The Tukey-test showed that TP had significant effects on this amplitude (p<0.05). On the other hand, no difference were observed in the percentage of PPI or in startle amplitude for the pre-TP and post-TP sessions, indicating a recover from stress in rats after the pinch was removed from the tail. In the startle amplitude of each

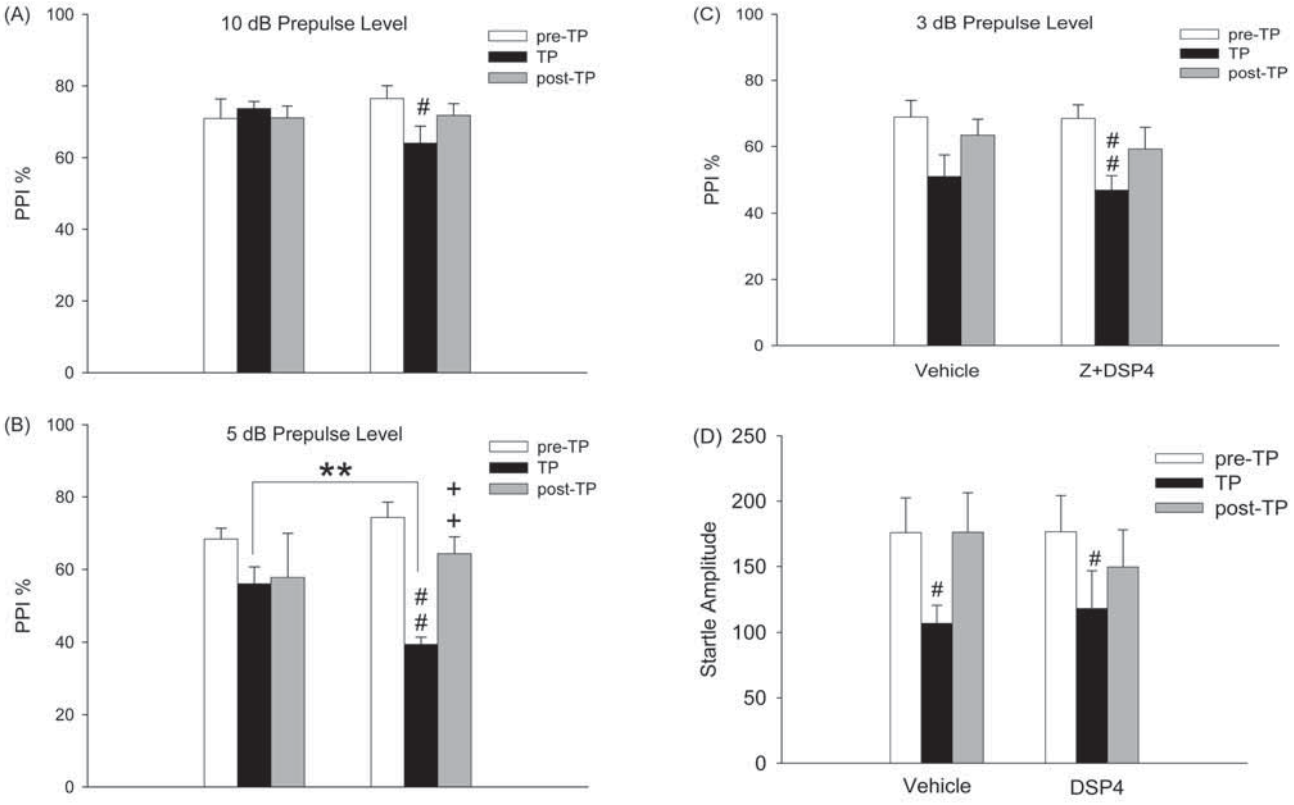


Fig. 2 Effects of DSP4 lesion on TP stress-induced changes in PPI of acoustic startle. The rats were separated into two groups, with DSP4 (zimeldine (Z)+DSP4) and without (vehicle) lesion. All other markers were identical to Figure 1 indications. Repeated one-way ANOVA showed a significant effect of tail-pinch on PPI% in DSP4-lesioned rats (a: $F(1,6)=10.22$, $p<0.05$; b: $F(1,6)=45.291$, $p<0.01$; c: $F(1,6)=27.061$, $p<0.01$) and startle amplitude in both vehicle and DSP4-lesioned rats (vehicle: $F(1,6)=8.472$, $p<0.05$; DSP-4: $F(1,6)=7.875$, $p<0.05$). A post hoc comparison of the group mean by a Tukey test indicated statistical significance (#) between TP and pre-TP stages or (+) between TP and post-TP stages. Further comparisons by Independent T-test showed the statistical significance (*) between vehicle and DSP4-lesioned rats at the TP session (b: ($t=3.278$, $p<0.01$). Values indicate the mean±SE. One symbol: $p<0.05$; two symbols: $p<0.01$.

prepulse (73, 75, 80 dBs)+pulse, the individual effect and the other two experiments of TP are summarized in Figure 5. In general, TP had no significant effect on the pair amplitudes presented in vehicle control rats (top figure).

**Effects of a DSP-4 Lesion of the DNEB on TP Stress-induced Changes in PPI of Acoustic Startle**

Effects of TP on startle responses and PPI in neurotoxin DSP4-lesioned rats are shown in Figure 2. ANOVA revealed a significantly disruptive effect of DSP4 lesions on the percentages of PPI responses (10 dB: $F(1,6)=10.22$, $p<0.05$; 5dB: $F(1,6)=45.291$, $p<0.01$; 3dB: $F(1,6)=27.061$, $p<0.01$). Tukey-test comparisons revealed that TP reduced PPI scores in vehicle control rats were significantly potentiated in rats with DSP4 lesions. In the TP session, the group of rats with DSP4 lesions was significantly less active in PPI scores than the control, vehicle-treated rats ($p<0.001$). Further comparisons by Independent T-test revealed that there were differences between groups, vehicle control vs. DSP4 lesions, in the TP session in the 5 dB prepulse level (75 dB) PPI reactivity ($t=3.278$, $p<0.01$). ANOVA also revealed significant effects of the TP on startle amplitude in both group rats (vehicle: $F(1,6)=8.472$, $p<0.05$; DSP-4: $F(1,6)=7.875$, $p<0.05$). On the other hand, no difference was observed in the percentage of PPI or startle amplitude for the pre-TP and post-TP sessions, indicating a recovery from stress in rats after the pinch was removed from the tail. Again, in the startle amplitude of each prepulse (73, 75, 80 dBs)+pulse pair, the individual effect of TP is summarized in Figure 5. There was a significant effect of TP on the 75 dB pair amplitude presented in DSP-4 lesion rats

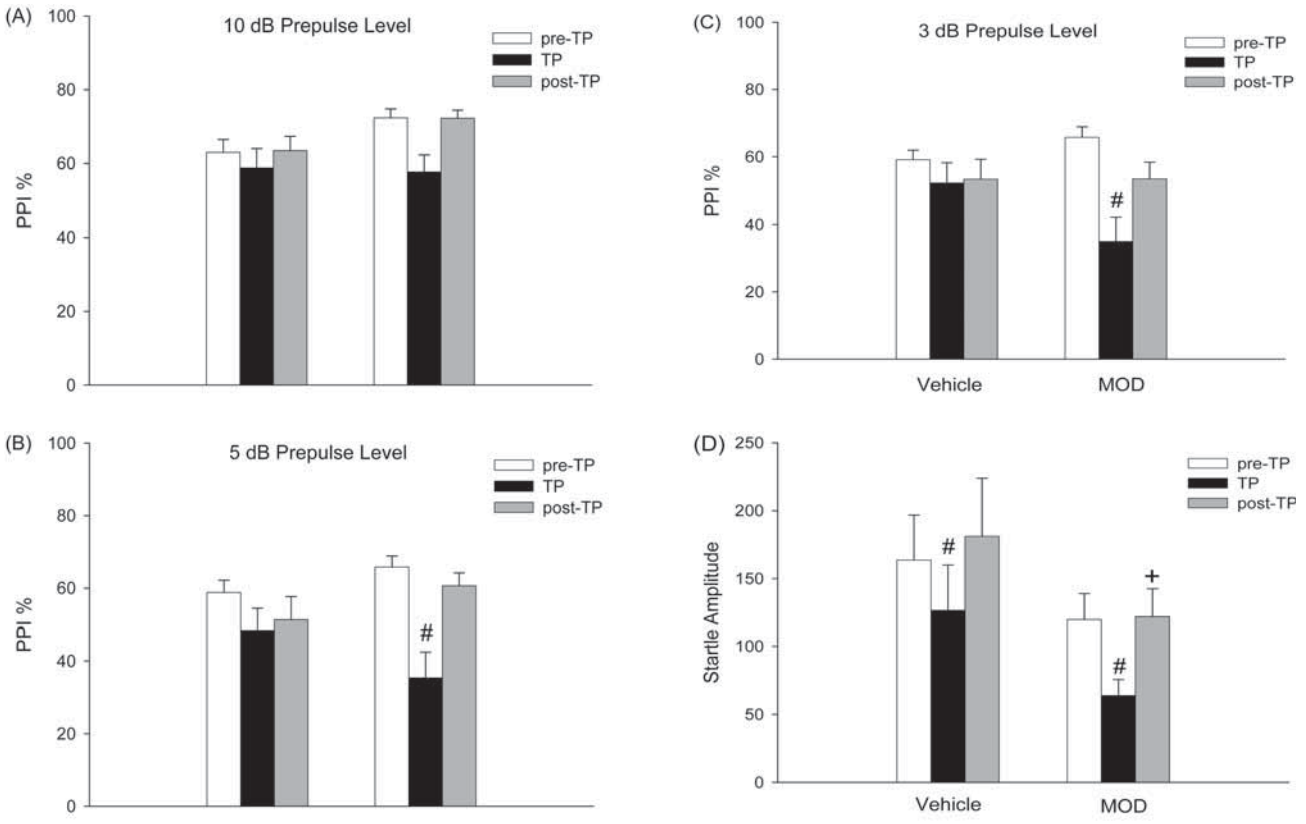


Fig. 3 Effects of modafinil pretreatment on TP stress-induced changes in PPI of acoustic startle. The rats were separated into two groups, modafinil (MOD)-pretreated rats and vehicle-pretreated rats. All other markers were identical to Figure 1 indications. Repeated one-way ANOVA showed a significant effect of tail-pinch on PPI% in modafinil-pretreated rats (b: $F(1,6)=7.558$, $p<0.05$; c: $F(1,6)=10.072$, $p<0.05$) and startle amplitude in both vehicle and DSP4-lesioned rats (vehicle: $F(1,6)=7.572$, $p<0.05$; modafinil: $F(1,6)=10.034$, $p<0.05$). A post hoc comparison of the group mean by a Tukey test indicated statistical significance (#) between TP and pre-TP stages or (+) between the TP and post-TP stages. Values indicate the mean $\pm$ SE. One symbol: $p<0.05$; two symbols: $p<0.01$.

(center figure).

**Effects of Modafinil Pretreatment on TP Stress-induced Changes in the PPI of Acoustic Startle**

Effects of TP on startle responses and PPI in modafinil-pretreated rats are shown in Figure 3. ANOVA revealed a significant disruptive effect of modafinil in the percentage of PPI responses only at relatively low prepulse levels (5dB: $F(1,6)=7.558$, $p<0.05$; 3dB: $F(1,6)=10.072$, $p<0.05$). Tukey-test comparisons revealed that TP reduced PPI scores in vehicle control rats were significantly potentiated in rats pretreated with modafinil. ANOVA also revealed a significant effect of the TP on startle amplitude in both group rats (vehicle: $F(1,6)=7.572$, $p<0.05$; modafinil: $F(1,6)=10.034$, $p<0.05$). On the other hand, no difference was observed in the percentage of PPI in the pre-TP and post-TP sessions, and a significantly higher startle amplitude of post-TP compared to TP session ($p<0.05$) was observed. These findings indicate a recovery from stress in rats after the pinch was removed from the tail. Once again, for startle amplitude of each prepulse (73, 75, 80 dBs)+pulse pair, the individual effect of TP stress is summarized in Figure 5. There was no significant effect of TP on the pair amplitudes presented in the modafinil pretreatment rats (bottom figure).

**Modulation of Modafinil Responses by Haloperidol**

As shown in Figure 4, haloperidol normalized modafinil-induced PPI reduction during TP sessions. In general, there was no significance in the percentages of PPI and pulse-alone startle magnitude throughout all the

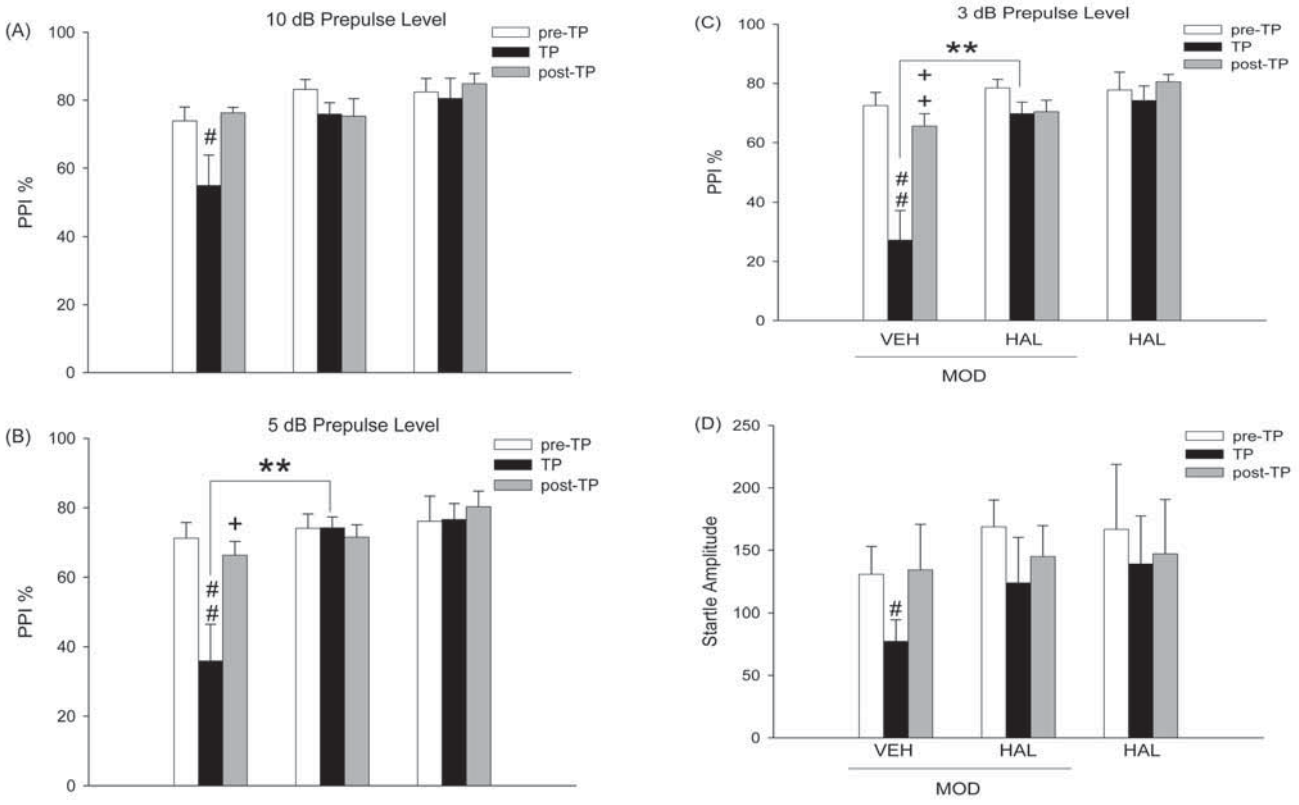


Fig. 4 Effects of haloperidol on PPI of acoustic startle of modafinil by TP stress. The rats were administered with vehicle (VEH) plus modafinil (MOD), haloperidol (HAL) plus modafinil (the middle three bars), or haloperidol plus vehicle (the right three bars). All other markers were identical to Figure 1 indications. Repeated one-way ANOVA showed a significant effect of tail-pinch on PPI% ((A): $F(1,6)=7.751$, $p<0.05$; (B): $F(1,6)=14.38$, $p<0.01$; (C): $F(1,6)=18.069$, $p<0.01$) and startle amplitude ((D): $F(1,6)=4.703$, $p<0.05$) in haloperidol plus modafinil rats (the middle three bars). A post hoc comparison of the group mean by a Tukey test indicated statistical significance (#) between TP and pre-TP stages or (+) between TP and post-TP stages. Further comparisons by Independent T-test showed the statistical significance (*) between vehicle plus modafinil and haloperidol plus modafinil (the middle three bars) rats at the TP session (b: ($t=3.278$, $p<0.01$); c: ($t=3.971$, $p<0.01$). Values indicate the mean$\pm$SE. One symbol: $p<0.05$; two symbols: $p<0.01$.

TP sessions in the haloperidol-alone group rats. ANOVA performed on the percentage of PPI revealed a significant PPI-disruptive effect (10 dB: $F(1,6)=7.751$, $p<0.05$; 5dB: $F(1,6)=14.38$, $p<0.01$; 3dB: $F(1,6)=18.069$, $p<0.01$) and a reduction of the pulse-alone startle magnitude ($F(1,6)=7.572$, $p<0.05$) throughout all the TP sessions in the vehicle plus modafinil-pretreated group rats. The effects of modafinil were reversed by haloperidol as shown in the haloperidol plus modafinil-pretreated group rats (all $p>0.05$). Further comparisons by Independent T-test revealed that there were differences between these two group of rats for TP sessions in the 3 dB and 5 dB prepulse level PPI responses (3dB: $t=3.971$, $p<0.01$; 5dB: $t=3.278$, $p<0.01$).

## DISCUSSION

The results from experiments 2 and 3 demonstrate that both modafinil pretreatment and DNEB lesions with neurotoxin DSP4 precipitate sensorimotor gating deficits in rats confronted by TP stress. A comparison between these two results is enlightening. The similar patterns of results in PPI suggest that NE, the main molecular target of many arousal-promoting substances, might be also involved in modafinil's effects. On the other hand, the results from experiment 4 show that co-treatment with haloperidol significantly reverts the TP-induced PPI reduction in modafinil pretreatment rats alone. This indicates that activation of DA neurons, particularly DA D2 receptors, still hold the prominent role in the effect of

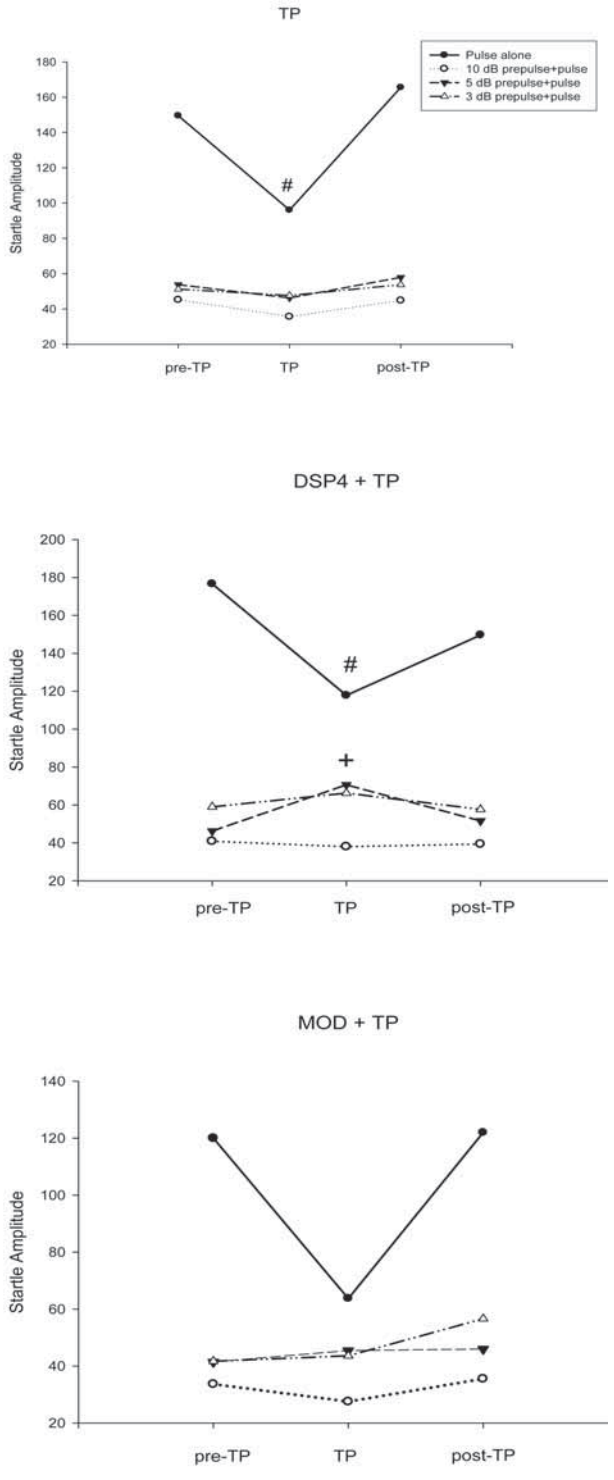


Fig. 5 Startle amplitude measured during an effect of TP stress (TP), an effect of TP stress following DSP4 lesions (DSP4+TP), and an effect of TP stress following an injection of modafinil (MOD+TP). The statistical significance symbols are indicated in other figures.

modafinil on PPI disruption.

Previous studies on rats have established the fact that sensorimotor gating is regulated by multiple dynamic neural interactions. Numerous forms of stressful management are known to produce this gating disturbance effectively.[32-33] Our initial experiment therefore sought to determine the effects of TP as a mild stressor model on startle responses and PPI. The results indicated that TP (Fig. 1) produced a significant decrease in pulse-alone startle amplitude and a declining trend. However, no was observed in PPI intensity. These results are consistent with previous reports that suggest that TP might alter sensorimotor gating reactivity to acoustic startle.[34]

TP are known to stimulate DA and NE overflows in several brain regions, including the medial prefrontal cortex, nucleus accumbens and striatum.[29,35-37] A great deal of evidence also indicates that in various brain regions, the catecholamine neuron activation in responses to TP is dissimilar; in addition, DA and NE projections are differentially regulated during ongoing behaviors.[36-39] For example, TP induced eating behavior is critically dependent on the nigrostriatal DA system.6 However, the NE projection to the medial prefrontal cortex has been suggested to be more responsive to stressful and rewarding stimuli than ones that innervate the striatum.[37-38,40]

It has also been reported that there are a number of circuits through which NE can influence DA activity, and it is known that such influence most likely occurs under a stressful environment.[29,41-43] The interaction between these two catecholamines might be linked directly or indirectly via mechanisms of synaptic stimulation or inhibition. Generally, the α-1 adrenoceptors are known to mediate the stimulatory influence of NE on nucleus accumbens DA, whereas DA D2 receptors are known to mediate the inhibitory influence of NE on ventral tegmental area DA.[29,44] In fact, there are regions where NE targets have been proven to contain DA innervations, such as nucleus accumbens and the ventral tegmental area. These regions are known to play the main role in sensorimotor gating regulations.[1,7] In addition, PPI is sensitive to NE influences. It has been reported that PPI is disrupted by the administration of the α-1 agonist, cirazoline.[45] Moreover, it has been reported the disruptive effects of PPI caused by the indirect DA agonist amphetamine are opposed by the NE reuptake inhibitor, desipramine.[46] All these indications prompted us to reevaluate the predictive role of NE in sensorimotor gating regulations. As a result, the second experiment was designed by using neurotoxin DSP4 to identify whether or not brain DNEB neurons are essential elements in the organization of this gating.

Our results indicate that TP elicited a significantly PPI-disruptive effect in neurotoxin DSP4-lesioned rats with a reduction of the pulse-alone startle magnitude but an elevation of the average prepulse plus pulse startle magnitude (Fig. 2). These findings are helpful in interpreting the possible role of NE on DA related startle mechanisms as either inhibitory or augmenting effects.[41] If there is an inhibitory interaction between NE and DA, the loss of inhibition from NE influences caused by DNEB lesions might augment the effects of TP on PPI by activation of the mesolimbic DA mechanisms. On the other hand, if there is integral circuitry linking both DNEB and VNEB pathways while a stimulatory NE-DA interaction exists, the effects to TP exposure by PPI disruption could result from an imbalance between DNEB and VNEB pathways. DNEB lesions might further increase the VNEB neuronal activities and then produce a stimulatory influence on the mesolimbic DA mechanisms.[47]

Approved by the FDA since 1998 for treating narcolepsy, the use of modafinil has expanded rapidly into the treatment of fatigue, depression, attention deficit hyperactive disorder, and sleepiness caused by other medicines. The effect of modafinil on the sensorimotor gating deserves notice because analogous psychostimulant drugs such as amphetamine and PCP result in an increased risk of PPI disruption[1,9,10] Consequently, we began in experiments 3 and 4 to investigate whether this drug, with or without the addition of TP, distorts the mechanisms of sensorimotor gating regulations in rats.

With a modafinil dose of 64 mg/kg, the test elicited a significant PPI-disruptive effect with a reduction of pulse-alone startle magnitude throughout all the TP sessions (Fig. 3). In contrast with the stressful status of TP on sensorimotor gating, modafinil had no effect in naive status (pre- or post-TP session). These results demonstrate the first evidence, to our knowledge, that modafinil is able to impair sensorimotor gating reactivity in animals, similar to the effects of other psychostimulant drugs.

It is worthy to note that the dose of modafinil used in present study is a typically reported dose for behavioral testing in other studies.[48] In our study, this dose produced the most reliable reduction in PPI, and the magnitude of reduction was higher (approximately 40-70%) than that of the neurotoxin DSP4-lesioned rats (approximately 30-60%). In contrast with the neurotoxin DSP4-lesioned group rats, however, on average, TP has no effect on the startle magnitude of prepulse plus pulse in modafinil pretreated group rats (Fig. 4). One interpretation of this difference is that the mechanisms of PPI underlying averseness exposure to TP along with administration of modafinil are incompletely affected by NE. It may be normal that DA is the primary substrate involving in sensorimotor gating regulations,[1] thus changes in mesolimbic DA activity are still the major mechanisms in modafinil's effects. We thus turn to examine this possibility via the fourth experiment. The results indicate that DA activity is truly important; DA D2 antagonist haloperidol reduces the effects of TP and completely antagonizes the effects of modafinil on PPI disruption. The masking effect of haloperidol due to a powerful D2 blockade is unlikely since no PPI disruption followed haloperidol administration in the pre-TP condition in all prepulse levels (see Figure 4).

Because of the similar patterns showing in the reduction of PPI in the administration of modafinil and the lesions of DNEB rats, we consider the possibility that common mechanism exists for these two types of management. We are tempted to speculate that the modafinil's effects on sensorimotor gating reactivity still require bonded brain NE neurons. However, it is still beyond our present results to make a conclusion about this relationship that NE is independently involved in modafinil-induced sensorimotor gating deficits. It is obvious that the role of DNEB in modafinil's effects would be strengthened considerably if a similar PPI paradigm could be applied in the neurotoxin DSP4-lesioned rats treated with modafinil. We already carried out such experiment. However, as of yet, the initial results are still insufficient to draw any conclusions.

In conclusion, our results have revealed several important points regarding the PPI paradigm used in the present experiments: (i) The averseness of TP exposure mildly alter sensorimotor gating reactivity to acoustic startle in rats. Two types of managements, pretreatment with modafinil and DNEB lesion, both augment the effects of TP on PPI disruption. (ii) The reversal of the modafinil-induced PPI reduction by haloperidol indicates that DA is the primary substrate for modafinil's effects. (iii) The profile of effects of modafinil is similar to that after DNEB lesions, indicating NE neurons might be involved in modafinil's effects. For wake-promoting purposes modafinil should be used with caution since it has potential to elicit PPI disruptive effects such as those of other psychostimulant drugs. Future studies still need to clarify the brain NE role in the effects of modafinil in sensorimotor gating reactivity. For example, to examine the effect of modafinil following DSP4 procedure could elucidate the relationship of DNEB and VNEB in this regard in a more detailed way.

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