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Effect of haloperidol on the behavioral stimulation by *N*-cyanomethylmethamphetamine, a main product of smoking methamphetamine mixed with tobacco

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Abstract

N-Cyanomethylmethamphetamine is a main product of smoking methamphetamine mixed with tobacco. The aim of this experiment was to evaluate the effects of haloperidol on behavioral stimulation by *N*-cyanomethylmethamphetamine (3 mg/kg s.c.) in terms of ambulation in mice. Repeated administration of *N*-cyanomethylmethamphetamine, carried out 5 × at 3-day intervals, induced a sensitization to its ambulation-increasing effect. Haloperidol (0.01, 0.03, 0.1 and 0.3 mg/kg s.c.) significantly inhibited not only the acute stimulant effect of *N*-cyanomethylmethamphetamine but also the induction of sensitization. The dose-effect curves for the inhibitory effects of haloperidol on the *N*-cyanomethylmethamphetamine-induced ambulatory stimulation were almost the same between the drug-naive and *N*-cyanomethylmethamphetamine-sensitized mice. Moreover, such behavioral characteristics of *N*-cyanomethylmethamphetamine; the behavioral stimulant effect, the induction of sensitization following repeated administration, and the inhibition of its effects by haloperidol, were qualitatively the same as those of methamphetamine (2 mg/kg s.c.). These results suggest that *N*-cyanomethylmethamphetamine possesses methamphetamine-like central stimulant effect and that D_2 dopaminergic mechanisms are involved in the effect of *N*-cyanomethylmethamphetamine.

Keywords: *N*-Cyanomethylmethamphetamine; Methamphetamine; Haloperidol; Behavioral sensitization; Ambulation; (Mouse)

1. Introduction

It has been reported that the repeated administrations of amphetamines induce a sensitization to their behavioral stimulant effect (e.g. Kilbey and Sannerud, 1985; Kuribara and Hirabayashi, 1985; Tadokoro and Kuribara, 1990), and that the sensitization is intimately related to the development of psychopathological symptoms after the repeated abuse of amphetamines, viz. amphetamine psychosis (Ellinwood and Kilbey, 1977; Tadokoro and Kuribara, 1986). There is no doubt that a certain change in the dopaminergic neurotransmission is responsible for the induction of sensitization, because of the inhibitory effect of dopamine receptor antagonists on the sensitization to amphetamines (Robinson and Becker, 1985; Kuribara and Uchihashi, 1993, 1994).

N-Cyanomethylmethamphetamine is a main product of smoking methamphetamine mixed with tobacco (Sekine and Nakahara, 1987, 1990; Sekine et al., 1995). It has been reported that *N*-cyanomethylmethamphetamine increases spontaneous motor activity at comparatively smaller doses, and induces stereotypy at higher doses in rodents (Nakahara and Sekine, 1987). However, it has been yet unclear whether the dopaminergic neurotransmission is involved in the behavioral stimulant effect of *N*-cyanomethylmethamphetamine, and whether the repeated administration of *N*-cyanomethylmethamphetamine induces behavioral sensitization.

The aim of this study was to evaluate modification by haloperidol, a prototypic butyrophenone antipsychotic with

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strong antagonistic action on dopamine D_2 receptors, of the effects of repeatedly administered *N*-cyanomethylmethamphetamine in terms of ambulation in mice. The results were compared with those after the combined administrations of methamphetamine with haloperidol.

2. Materials and methods

2.1. Animals

Male mice of the dd strain (Institute of Experimental Animal Research, Gunma University School of Medicine, Maebashi) were used at 6 weeks of the age and weighing 25–30 g. Throughout the experimental period, the mice were group housed (10 mice each) in polycarbonate cages (25 W × 20 D × 15 H cm) in a controlled room (temperature: 23 ± 2°C; relative humidity: 55 ± 2%; and a 12-h : 12-h light : dark schedule, light period between 06:00 and 18:00 h). They could freely access to a solid diet (MF: Oriental Yeast, Tokyo) and tap water except during the times of behavioral test.

2.2. Apparatus

The ambulations of individual mice were measured with a tilting-type ambulometer having 10 bucket-like activity cages of 20 cm in diameter (SMA-10: O'Hara & Co., Tokyo). Horizontal movements of the mouse generated tilts of the activity cage, and they were detected with microswitches attached to the cage. Such mechanical characteristics enabled to selectively record the ambulations, but not the vertical movements.

2.3. Drugs

The drugs used were *N*-cyanomethylmethamphetamine HCl (synthesized by us), methamphetamine HCl (Philopon; Dainippon Pharmaceuticals, Osaka) and haloperidol (Serenace Inj.; Dainippon Pharmaceuticals). The commercial preparation of haloperidol was diluted, and *N*-cyanomethylmethamphetamine and methamphetamine were dissolved with the physiological saline, and administered s.c. Since *N*-cyanomethylmethamphetamine in aqueous solution was unstable, the solution of *N*-cyanomethylmethamphetamine was made immediately before the injection. The concentration of each drug solution was adjusted so that the volume injected was always constant at 0.1 ml/10 g body weight of the mouse. Since our previous study showed that the stimulant effect of *N*-cyanomethylmethamphetamine was estimated to be 2/3 × as potent as that of methamphetamine (Kuribara et al., 1996; Sekine et al., submitted), the doses of *N*-cyanomethylmethamphetamine and methamphetamine were fixed to 3 and 2 mg/kg, respectively. These doses were also considered to be optimum for increase in the ambulation of dd mice without eliciting a strong stereotypy (Hirabayashi and Alam, 1981; Kuribara et al., 1996).

2.4. Experimental procedures

In each experiment described below, the drug administration was conducted after an adaptation of the mouse to the activity cage for 0.5 h, and it was followed by the measurement of ambulation for 3 h. All the experiments were carried out between 09:00 and 16:00 h.

2.4.1. Experiment 1

Five groups of mice (10 each) were given one of the following 5 × -repeated administrations at 3-day intervals: *N*-cyanomethylmethamphetamine alone, and the combinations (simultaneous administration) of *N*-cyanomethylmethamphetamine with haloperidol (0.01, 0.03, 0.1 and 0.3 mg/kg). Three days after the fifth drug administration, *N*-cyanomethylmethamphetamine alone was challenge-administered to all of these mice.

The other 5 groups of mice were given either methamphetamine alone or the combination of methamphetamine with haloperidol (0.01, 0.03, 0.1 or 0.3 mg/kg) 5 × at 3-day intervals. Three days after the fifth drug administration, all of these mice were challenged with methamphetamine.

2.4.2. Experiment 2

Two sets of 5 groups of mice (10 each) were first treated with the 5 × -repeated administrations of either *N*-cyanomethylmethamphetamine or methamphetamine at 3-day intervals which induced the sensitization to individual drugs (see Results). Three days after the fifth administration, the mice treated with *N*-cyanomethylmethamphetamine were challenged with either *N*-cyanomethylmethamphetamine alone or combination of *N*-cyanomethylmethamphetamine with haloperidol (0.01, 0.03, 0.1 or 0.3 mg/kg). The mice treated with methamphetamine were challenged with methamphetamine alone or combination of methamphetamine with haloperidol (0.01, 0.03, 0.1 or 0.3 mg/kg).

2.5. Statistical analysis

The mean 3-h overall ambulatory activity counts were first analysed by two-way ANOVA. The factors were the doses of haloperidol (5 levels including *N*-cyanomethylmethamphetamine or methamphetamine alone as the dose = 0), the number of administrations (5 levels), and the treatments (the drug-naive and the *N*-cyanomethylmethamphetamine- or methamphetamine-sensitized). In the cases of significant overall variance, posthoc analyses were carried out by Dunnett's test. P values of < 0.05 were considered significantly different.

3. Results

3.1. Experiment 1

3.1.1. N-Cyanomethylmethamphetamine study

Fig. 1 shows the mean 3-h overall activity counts after 5 × -repeated administrations of *N*-cyanomethylmethamphetamine alone and combinations of *N*-cyanomethylmethamphetamine with haloperidol. The repeated administration of *N*-cyanomethylmethamphetamine alone induced a progressive enhancement of its ambulation-increasing effect, and these effects were inhibited by haloperidol. Thus, the activity counts were significantly dependent on haloperidol dose [$F(4,225) = 130.6$, $P < 0.001$] and administration number [$F(4,225) = 14.8$, $P < 0.001$]. There was a significant haloperidol dose × administration number interaction [$F(16,225) = 6.9$, $P < 0.001$]. Posthoc analyses revealed that all the doses of haloperidol significantly inhibited the stimulant effect of *N*-cyanomethylmethamphetamine throughout the 5 × administrations. Furthermore, except for the administrations of *N*-cyanomethylmethamphetamine alone and the combination of *N*-cyanomethylmethamphetamine with 0.01 mg/kg haloperidol, the repeated administration of combinations of *N*-cyanomethylmethamphetamine with 0.03–0.3 mg/kg haloperidol did not elicit significant enhancement of the activity counts.

In the challenge administration of *N*-cyanomethylmethamphetamine, the activity counts of the mice given the combinations of *N*-cyanomethylmethamphetamine with 0.01–0.3 mg/kg haloperidol were significantly lower than that of the mice given *N*-cyanomethylmethamphetamine alone [$F(4,45) = 31.3$, $P < 0.001$], and these counts were almost the same as that of the drug-naive mice (Fig. 2).

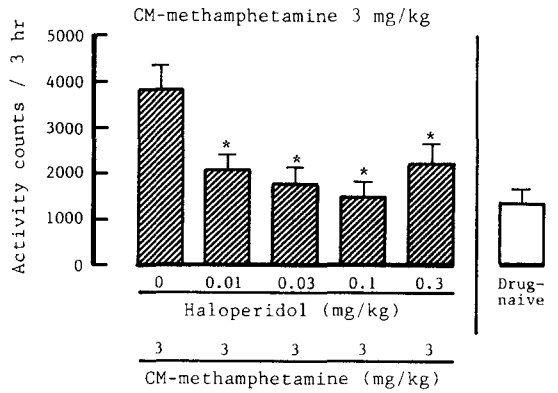

Fig. 2. Mean 3-h overall ambulatory activity counts with S.E.M. values after challenge administration of *N*-cyanomethylmethamphetamine (CM-methamphetamine: 3 mg/kg s.c.) to the mice pretreated with either *N*-cyanomethylmethamphetamine alone (haloperidol dose = 0) or combination of *N*-cyanomethylmethamphetamine with haloperidol (0.01, 0.03, 0.1 or 0.3 mg/kg) 5× at 3-day intervals. The challenge administrations were carried out 3 days after the fifth pretreatment. * $P < 0.05$ vs. the mice given *N*-cyanomethylmethamphetamine alone. $n = 10$ in each group.

3.1.2. Methamphetamine study

As shown in Fig. 3, repeated administration of methamphetamine also induced a progressive enhancement of its ambulation-increasing effect, and was significantly inhib-

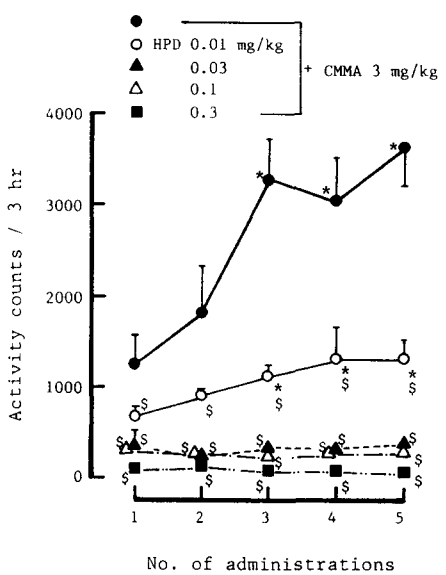

Fig. 1. Mean 3-h overall ambulatory activity counts with S.E.M. values after 5×-repeated s.c. administrations of *N*-cyanomethylmethamphetamine (CMMA: 3 mg/kg) alone (haloperidol dose = 0) and combinations of *N*-cyanomethylmethamphetamine with haloperidol (0.01, 0.03, 0.1 and 0.3 mg/kg) at 3-day intervals. * $P < 0.05$ vs. the first administration within each group of mice. $ $P < 0.05$ vs. the mice given *N*-cyanomethylmethamphetamine alone in the same administration number. $n = 10$ in each group.

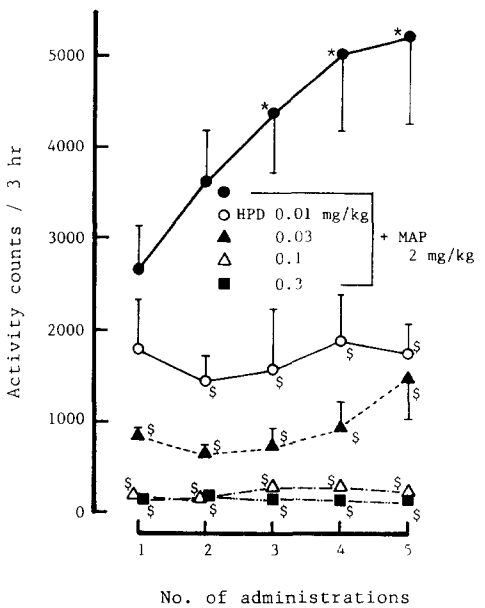

Fig. 3. Mean 3-h overall ambulatory activity counts with S.E.M. values after 5×-repeated s.c. administrations of methamphetamine (MAP: 2 mg/kg) alone (haloperidol [HPD] dose = 0) and combinations of methamphetamine with haloperidol (0.01, 0.03, 0.1 and 0.3 mg/kg) at 3-day intervals. * $P < 0.05$ vs. the first administration within each group of mice. $ $P < 0.05$ vs. the mice given methamphetamine alone. $n = 10$ in each group.

ited by haloperidol [$F(4,225) = 168.0$ and $F(4,225) = 9.2$ for haloperidol dose and administration number, respectively, $P < 0.001$]. There was a significant haloperidol dose × administration number interaction [$F(16,225) = 3.4$, $P < 0.01$]. Posthoc analyses revealed that, except for the first combined administration of methamphetamine with 0.01 mg/kg haloperidol, all the other combinations resulted in significantly lower activity counts than those following the administrations of methamphetamine alone. Moreover, the combined administrations of methamphetamine with haloperidol did not produce any significant enhancements of the activity count.

As shown in Fig. 4, in the challenge administration of methamphetamine, the activity counts of mice given the combinations of methamphetamine with 0.01–0.3 mg/kg haloperidol were significantly lower than that of the mice given methamphetamine alone [$F(4,45) = 39.2$, $P < 0.001$], and these counts were almost the same as that of the drug-naive mice.

3.2. Experiment 2

3.2.1. N-Cyanomethylmethamphetamine study

Fig. 5 shows the dose-effect relationships of activity counts for the combined administrations of *N*-cyanomethylmethamphetamine with haloperidol in the drug-naive and *N*-cyanomethylmethamphetamine-sensitized mice. The data of the drug-naive mice were the same as those presented in Fig. 1 (the data in the first administration). The ambulation-increasing effect of *N*-cyanomethylmethamphetamine was reduced by haloperidol, and the changes were significantly dependent on haloperidol dose and condition (i.e. drug-naive and *N*-cyanomethylmethamphetamine-sensitized) [$F(4,90) = 69.0$ and $F(1,90) = 35.1$, respectively, $P < 0.001$]. However, there was no significant haloperidol × condition interaction [$F(4,90) = 1.2$, N.S.]. Posthoc analyses revealed that 0.01–0.3 mg/kg haloperidol significantly inhibited *N*-cyanomethylmethamphetamine-induced ambulatory stimu-

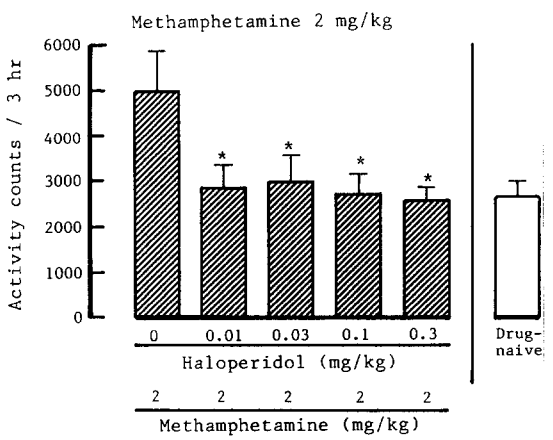

Fig. 4. Mean 3-h overall ambulatory activity counts with S.E.M. values after challenge administration of methamphetamine (2 mg/kg s.c.) to the mice pretreated with either methamphetamine alone (haloperidol dose = 0) or combination of methamphetamine with haloperidol (0.01, 0.03, 0.1 or 0.3 mg/kg) 5× at 3-day intervals. The challenge administrations were carried out 3 days after the fifth pretreatment. * $P < 0.05$ vs. the mice given methamphetamine alone. $n = 10$ in each group.

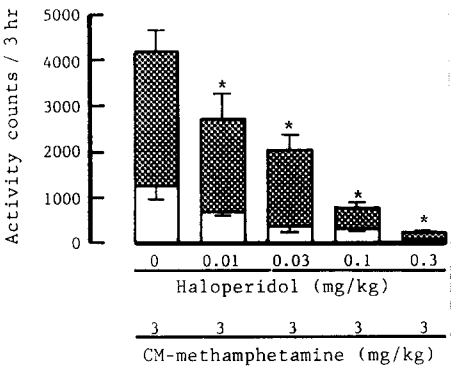

Fig. 5. Mean 3-h overall ambulatory activity counts with S.E.M. values after combined (simultaneous) s.c. administrations of *N*-cyanomethylmethamphetamine (CM-methamphetamine: 3 mg/kg) with haloperidol (0–0.3 mg/kg) to the drug-naive mice (open band) and *N*-cyanomethylmethamphetamine-sensitized mice (open band + stippled band). The data of drug-naive mice were the same as those presented in Fig. 1 (the first administration). The *N*-cyanomethylmethamphetamine-sensitized mice had been treated with 5×-repeated administrations of *N*-cyanomethylmethamphetamine (3 mg/kg) at 3-day intervals and the challenge with combined administration was carried out 3 days after the fifth pretreatment with *N*-cyanomethylmethamphetamine. * $P < 0.05$ vs. the administration of *N*-cyanomethylmethamphetamine alone (haloperidol dose = 0) in both the drug-naive and *N*-cyanomethylmethamphetamine-sensitized mice. $n = 10$ in each group.

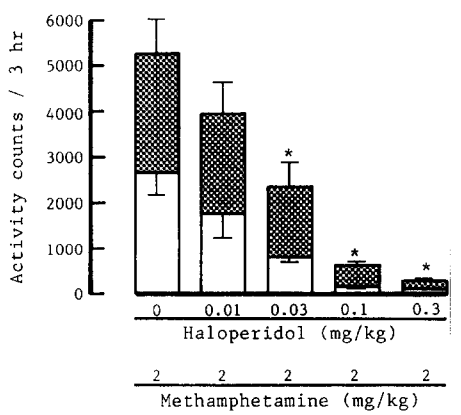

Fig. 6. Mean 3-h overall ambulatory activity counts with S.E.M. values after combined (simultaneous) s.c. administration of methamphetamine (2 mg/kg) with haloperidol (0–0.3 mg/kg) to the drug-naive mice (open band) and methamphetamine-sensitized mice (open band + stippled band). The data of drug-naive mice were the same as those presented in Fig. 3 (the first administration). The methamphetamine-sensitized mice had been pretreated with the 5×-repeated administrations of methamphetamine (2 mg/kg) at 3-day intervals and the challenge with combined administration was carried out 3 days after the fifth pretreatment with methamphetamine. * $P < 0.05$ vs. the administration of methamphetamine alone (haloperidol dose = 0) in both the drug-naive and methamphetamine-sensitized mice. $n = 10$ in each group.

lation in both the drug-naive and *N*-cyanomethylmethamphetamine-sensitized mice.

3.2.2. Methamphetamine study

As shown in Fig. 6, in both the drug-naive and methamphetamine-sensitized mice, the ambulation-increasing effect of methamphetamine was reduced by haloperidol [$F(4,90) = 70.1$ and $F(1,90) = 28.7$ for haloperidol dose and condition, respectively, $P < 0.001$]. There was no significant haloperidol dose × condition interaction [$F(4,90) = 0.8$, N.S.]. Posthoc analyses revealed that 0.03–0.3 mg/kg haloperidol significantly reduced the effect of methamphetamine in both the drug-naive and methamphetamine-sensitized mice.

4. Discussion

The present experiment demonstrated methamphetamine-like central stimulant effect of *N*-cyanomethylmethamphetamine. Thus, 3 mg/kg *N*-cyanomethylmethamphetamine and 2 mg/kg methamphetamine significantly increased the ambulation of mice, and the effects were progressively enhanced by 5 × -repeated administrations at 3-day intervals. The results of methamphetamine study were consistent with our previous reports (e.g. Kuribara and Uchihashi, 1993).

It has been considered that a change in the dopaminergic neurotransmission is involved in the induction of sensitization to amphetamine-like drugs (Robinson and Becker, 1985). This consideration can also be applied to the sensitization to *N*-cyanomethylmethamphetamine. This is because haloperidol, a prototypic butyrophenone antipsychotic having a strong antagonistic action on dopamine D_2 receptors, inhibited the ambulation-increasing effect of *N*-cyanomethylmethamphetamine in a dose-dependent manner throughout the 5 × -repeated administrations. Similar antagonistic interaction was demonstrated in the combination of methamphetamine with haloperidol in this study, and amphetamines with various kinds of antipsychotics (see review by Worms et al., 1983). Although the activity counts were quantitatively different following the administrations of *N*-cyanomethylmethamphetamine and methamphetamine alone, the dose-effect curves for the antagonistic effects of haloperidol on both the *N*-cyanomethylmethamphetamine- and methamphetamine-induced ambulatory stimulation were qualitatively the same. These results indicate that the blockade of postsynaptic dopamine receptors, particularly D_2 subtype, can effectively inhibit the stimulant effect of both *N*-cyanomethylmethamphetamine and methamphetamine.

The involvement of dopaminergic neurotransmission in the induction of sensitization to *N*-cyanomethylmethamphetamine and methamphetamine was also confirmed by the inhibitory effect of haloperidol thereon. Thus, during the 5 × -repeated administrations, the combined administration of *N*-cyanomethylmethamphetamine or methamphetamine with haloperidol did not produce progressive enhancement of the ambulatory stimulation, except for the combination of *N*-cyanomethylmethamphetamine with 0.01 mg/kg haloperidol. The results following the combined administration of methamphetamine with haloperidol were in agreement with the previous report (Kuribara and Uchihashi, 1993). A similar inhibition of the sensitization has also been observed following the combined administration of methamphetamine with nemonapride, a potent and selective dopamine D_2 receptor antagonist of benzamide derivative (Kuribara and Tadokoro, 1990; Kuribara and Uchihashi, 1994).

Furthermore, the present experiment demonstrated that the mice given the combined administration of either *N*-cyanomethylmethamphetamine or methamphetamine with 0.01–0.3 mg/kg haloperidol did not exhibit increased sensitivities to challenge-administered *N*-cyanomethylmethamphetamine and methamphetamine, respectively. These results clearly indicate that haloperidol is effective for inhibition of induction of behavioral sensitization to both *N*-cyanomethylmethamphetamine and methamphetamine. The inhibitory effect of haloperidol on the methamphetamine sensitization was almost the same as that demonstrated in our previous study (Kuribara and Uchihashi, 1993). These results indicate again that *N*-cyanomethylmethamphetamine possesses methamphetamine-like central stimulant effect.

The sensitization to amphetamines has been considered to be intimately related to the development of the psychopathological symptoms, viz. amphetamine psychosis, which is easily induced by the repeated abuse of amphetamines (Ellinwood and Kilbey, 1977; Tadokoro and Kuribara, 1986, 1990). Like methamphetamine, the repeated administration of *N*-cyanomethylmethamphetamine induced the behavioral sensitization, and it was protected by the combined administration of haloperidol in each administration. It is therefore concluded that repeated abuse of *N*-cyanomethylmethamphetamine (i.e. the smoking methamphetamine mixed with tobacco) has a risk of induction of a psychopathological symptoms which is similar to that produced by the abuse of amphetamines (Ellinwood and Kilbey, 1977; Tadokoro and Kuribara, 1986, 1990). It is considered that the psychopathological symptoms caused by abuse of *N*-cyanomethylmethamphetamine are induced by a repeated stimulation of dopaminergic neurotransmission through acceleration of the release and inhibition of the reuptake of dopamine at the presynaptic terminals that are same mechanisms as those of abuse of amphetamine-like drugs (McMillen, 1983).

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