Earlier concepts on the central action of procaine appear to have been limited to such untoward effects as restlessness, tremor and convulsion. Clinical experiences during the past decade, however, have revealed the usefulness of procaine as an analgesic when administered intravenously in a nontoxic dose. Bigelow and Harrison (1) evidenced this effect experimentally by the measurement of cutaneous pain threshold in human subjects. As Goodman (8) and Keats et al. (15) pointed out, such an action cannot be attributed to the local action on sensory nerves, since the concentration of procaine in the peripheral tissue should be far below the minimal concentration necessary for nerve block. This naturally leads to the concept that the central nervous system should be responsible for the procaine analgesia.

Despite the wide clinical uses of intravenous procaine (9), there has been no investigator who found pharmacologically any distinct action of procaine on the central nervous system, except excitatory effects, in experimental animals. The present investigation is an attempt to discover depressant effects of procaine on the central nervous system in a nontoxic dose. The yielded results seem to be sufficient to convince us of the variegated central actions of this drug.

METHODS

All experiments were performed in unanesthetized rabbits weighing 2-3 kg. Procaine hydrochloride usually in one per cent solution was injected intravenously, intracisternally (cisterna magna) or intraarterially (vertebral artery). Experimental techniques in detail will be described in each part of the subsequent section.

RESULTS

1. Changes of behavior

Unanesthetized and unfastened rabbits were carefully observed of their behavior as well as posture before and after the administration of procaine.

Rapid intravenous injection. Following the rapid intravenous injection of procaine in the dose of 10-15 mg/kg, excitements such as tremor, restlessness or clonic convulsion
were produced just as described in any textbook of pharmacology.

**Slow intravenous injection.** Following the intravenous injection of procaine in the dose of 10-15 mg/kg in a very slow rate such as 2 mg/minute, a depressed state was often observed instead of excitement. Although the intensity of the depression was varied individually, muscle tonus was more or less decreased, spontaneous activity was lost and the reposition from a passive side position was retarded. The duration of the effect was rather transient and subsided within 5-10 minutes. This central depressant effect of procaine could not attributed to a cardiovascular action, since no hypotensive effect in the arterial pressure was observable in this method of application. Many investigators might have neglected such a depression because of its unpredictable and transient appearance.

**Intracisternal injection.** A more prominent depressed state was manifested by the intracisternal injection of procaine in the dose of 0.25-0.5 mg/kg which corresponds to 1/20-1/60 of the intravenous dose. Lost spontaneous activity, ataxia in gait and retarded reposition from a passive recumbancy appeared in a few minutes and persisted for 10-15 minutes. Doses larger than 2 mg/kg resulted usually in a respiratory failure.

The central depressant effect of procaine in a nonexcitatory dose was remarked also in mice by Tanaka (23), who studied on the neurotoxicity according to the method described by Swinyard et al. (21) and calculated the intraperitoneal TD$_{50}$ (dose causing neurological deficit in 50 per cent of animals) as 105 mg/kg, whereas the excitatory dose was found over 120 mg/kg.

### 2. Abolishment of tonic extensor component of maximal electroshock seizure

The electroshock apparatus described by Woodbury and Davenport (25) was employed for inducing supramaximal electroshock seizure in rabbits. Through needle electrodes inserted into hypoderma close to each eye, 300 mA of current was delivered for 0.2 seconds. Abolishment of the hindlimb tonic extensor component of the seizure was regarded as the sign of anticonvulsant activity.

Procaine was injected intravenously half a minute prior to electroshock. The anticonvulsant activity as measured by the maximal electroshock method is shown in Table 1. The ED$_{50}$ (effective dose in 50 per cent of animals) was calculated by the

<table>
<thead>
<tr>
<th>Dose of procaine (mg/kg)</th>
<th>No. of animal protection</th>
<th>No. of animal tested</th>
<th>ED$_{50}$ (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>0/5 (0 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.7</td>
<td>3/8 (38 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>4/8 (50 %)</td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>2.0</td>
<td>7/8 (88 %)</td>
<td></td>
<td>(0.64–1.40)*</td>
</tr>
<tr>
<td>5.0</td>
<td>5/5 (100 %)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 95% confidence limits

**TABLE 1. Protecting effect of intravenous procaine on the tonic extensor phase of maximal electroshock seizure**
method of Litchfield and Wilcoxon (18) as approximately 1 mg/kg. Intracisternal procaine in the dose of 0.5 mg/kg was also capable of abolishing the tonic extensor phase. These effects, however, were of short duration and in most cases they subsided within 10 minutes after intravenous and 20 minutes after intracisternal injection.

Such an anticonvulsant property of procaine in rabbits has been found first by one of us, Yasukata (26), and the expanded study has been performed in mice statistically by Tanaka (23), who found intraperitoneal ED$_{50}$ was 45 mg/kg.

3. **Inhibition of nicotine tremor**

A rapid intravenous injection of nicotine in the dose of 0.35 mg/kg caused characteristic tremor of extremities interposing clonic convulsions. When procaine was administered intravenously in the dose of 5-10 mg/kg prior to the nicotine injection, tremor and convulsion were completely suppressed.

Cahen and Lynes (4) once reported this effect of procaine but they presumed that it might be due to the peripheral neuromuscular blocking action, probably hesitating to attribute it to a central effect. Now that many striking central actions of procaine are evidenced, there would be no reason to exclude the antitremor activity from them.

4. **Marked depressant effect in decorticate rabbits**

Bilateral ablation of cerebral hemisphere involving striate body and occasionally a part of thalamus was performed in unanesthetized rabbits. Following the operation the animal was merely watched for 2-3 hours. In this period the animal maintained normal posture and almost normal reflexes. “Sham rage” or exciting response to painful stimuli was elicited often but not necessarily.

Procaine was injected intravenously in the dose of 10 mg/kg 2-3 hours after the operation. Soon after the injection the animal looked extremely drowsy and then it took lateral recumbant position spontaneously or passively. Tapping the body with hand or other minor stimulations were unable to awake the animal for 10-30 minutes. When recovered from the recumbant position, the animal still showed drowsiness for about 20 minutes. During these depressed states “sham rage” or exciting response to stimuli was completely suppressed. Since the applied dose was able to produce only a slight depression in the intact animal (see the afore-mentioned article No. 1), it is obvious that procaine exerts a strong depressant action in the decorticate animal.

This result seems to have some connection with the remarkable finding of Dasgupta et al. (6), who reported a conspicuous depression induced by a minimal dose of chlorpromazine in decorticate cats. A similar depressant effect of benadryl in such a dose as has no effect in normal animals was found by us recently (19). The similarity between procaine and antihistaminics will be discussed in the subsequent section (see DISCUSSION).
5. Cardiovascular effect of procaine applied to the central nervous system

Pressure of carotid artery and respiration through tracheal cannula in the unanesthetized rabbit were recorded on the smoked drum. Procaine injected intracisternally in the dose of 0.5 mg/kg produced ordinarily a pressure rise of 40-100 mmHg accompanying some bradycardia and respiratory inhibition. Doses higher than 1 mg/kg resulted in a pressure fall. Tachyphylaxis was not observed following repeated intracisternal injections of procaine. The pretreatment with an anesthetic dose of hexobarbital sodium inverted the procaine hypertension to a hypotensive response, whereas morphine enhanced the pressor reaction to intracisternal procaine.

Injection of procaine into vertebral artery in the dose of 2 mg/kg caused a pressure rise similarly but accompanying a respiratory stimulation. Following ablation of cerebral hemisphere as well as diencephalon, i.e. in the midbrain animal, the pressor response to procaine was inverted to a hypotensive reaction and the respiratory stimulation was reversed to an inhibition. These facts suggest that procaine might fundamentally depress medullary centers whereas in the intact animal it might cause some unbalance, which results in a hypertension, of circulatory regulating mechanism in hypothalamus.

6. Inhibitory effect on the corneal reflex

Intensity of the corneal reflex in rabbits was measured by stimulating with hairs of different kinds of strength. Intravenous procaine in the dose of 10 mg/kg inhibited the reflex for 10-15 minutes, whereas intracisternally injected procaine in the dose of 0.5 mg/kg caused more marked inhibition of the reflex for 20 minutes. The summarized results are shown in Table 2.

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Dose of procaine (mg/kg)</th>
<th>Time following the injection (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0   1   3   5   10   15   20   30</td>
</tr>
<tr>
<td>Intravenous injection</td>
<td>5</td>
<td>---  ---  ---  ---  ---  ---  ---  ---</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>---  +  +  +  +  +  ---  ---</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>---  +  +  ++  ++  ++  ++  ---</td>
</tr>
<tr>
<td>Intracisternal injection</td>
<td>0.25</td>
<td>---  ---  ---  ---  ---  ---  ---  ---</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>---  +  +  ++  ++  ++  ++  ---</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>---  +  +  ++  ++  ++  ++  ---</td>
</tr>
</tbody>
</table>

Each mark is derived from the mean of tests in 3 animals.
- represents normal reflex
± retardation of reflex
+ slight inhibition of the reflex
++ marked inhibition of the reflex
These data indicate that the reflex inhibitory effect of procaine injected intravenously may be attributed to a central action of this drug, since, as has already been stated, the tissue concentration of procaine injected intravenously should be too dilute to block peripheral nerves or ganglions.

7. Inhibitory effect on the central pathway of Bezold reflex

This subject has been reported by our group separately elsewhere (13).

DISCUSSION

Many features of the action of procaine on the central nervous system are demonstrated by the present investigation. Particularly, the ability to modify the electrically induced convulsion, the marked depressant effect in decorticate animals and the inhibitory effects on several reflexes following intracisternal administration should be sufficient to evidence the existence of central depressant actions of procaine.

As some investigators have remarked (2, 3) actions of procaine resemble those of antihistaminics like dephenhydramine (benadryl) in many respects. The ability of benadryl to abolish the tonic extensor seizure was reported by Swinyard et al. (22); the potentiated depression by benadryl in decorticate animals was found in our laboratory (19) and the inhibitory effects of benadryl injected intravenously as well as intracisternally on the corneal reflex were reported by Hirose (12). Besides the well known antihistaminic action of procaine and the local anesthetic action of antihistaminics, both drugs inhibit the Bezold reflex (7, 17), antagonize the nicotine tremor (16), depress the cough reflex (14) and decrease the vagus effect (11).

Resemblances between the action of procaine and that of chlorpromazine, which is essentially a derivative of antihistaminics, are also recognizable. Comparing the systemic action of procaine reported by Hazard (10) and Sakai (20), involving the present study with those of chlorpromazine reported by Courvoisier et al. (5) or other investigators, one could easily realize how analogous a property the both drugs have in common. From the standpoint of chemical structure, procaine, antihistaminics and chlorpromazine arc common in having arylalkyl-tertiary amine. Recently Tanaka and Kawasaki (24) have pointed out that many substances belonging to this common structure have the ability to abolish the tonic extensor phase of maximal electroshock seizure. The whole action of procaine would be comprehensible from their opinion that these substances are more or less local anesthetic, antihistaminic, anticholinergic, spasmylytic, ganglioplegic, reflex inhibitory, antifibrillant, antiphlogistic, antipyretic, analgesic, antiemetic, hypnotic and anticonvulsant.

SUMMARY

1. Effects of procaine on the central nervous system were explored in unanesthetized rabbits.

2. Intracisternally injected procaine produced a depressed state in behavior; the
similar effect was observable following a slow intravenous injection, whereas a rapid intravenous injection caused an excitement.

3. Intravenous as well as intracisternal procaine abolished the tonic extensor phase of maximal electroshock seizure in a nontoxic dose.

4. Nicotine tremor was suppressed by the pretreatment with intravenous procaine.

5. Intravenous procaine produced a marked depression in decorticate animals.

6. Procaine injected into vertebral artery resulted in a rise of blood pressure accompanying respiratory stimulation. This was inverted to a hypotensive and hypopneic response following the transection of brain in the collicular level.

7. Corneal reflex was inhibited by intravenous or intracisternal procaine.

8. Evidences of central depressant effects of procaine were discussed and resemblances between procaine and antihistaminics were emphasized.

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