Effects of Chlorpromazine in the Nucleus Reticularis Lateralis on the Cat Cerebellar Potentials

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Abstract—In the experiments reported here, we investigated chlorpromazine (CPZ)-induced enhancement of the cat cerebellar potentials evoked by peripheral nerve stimulation, with regard to the subtypes of adrenoceptor in the nucleus reticularis lateralis (LRN). Electrical stimulus of the locus coeruleus (LC) at high frequencies enhanced cerebellar potentials evoked by peripheral nerve stimulation. Although similar stimulus increased them after pretreatment with an α2-antagonist, yohimbine, these enhancements were not recognized by pretreatment with an α1-antagonist, prazosin. Microinjection of norepinephrine (NE: 10 μg) into LRN decreased cerebellar potentials, and conversely, 30 μg of NE significantly increased them. Although microinjection of an α2-adrenoceptor agonist, clonidine, into the LRN depressed cerebellar potentials, clonidine-induced decrease was obviously antagonized by pretreatment with CPZ. Furthermore, an α1-adrenoceptor agonist, phenylephrine, into the LRN increased cerebellar potentials. Pretreatment with CPZ hardly changed phenylephrine-induced enhancement. We thought that CPZ blocked α2-autoreceptors in adrenergic terminals from the LC rather than α1-adrenoceptors within the LRN. As a result, NE released from the LC terminals may act on α1-adrenoceptors in the LRN and may attenuate activities of the LRN. Therefore, it was clear that previous CPZ-induced enhancement may be due to depression of the descending inhibitory adrenergic system via CPZ-induced blockade of α2-autoreceptors.

We have been studying effects of several drugs on the cerebellum. In previous studies (1), we examined actions of central nervous system depressants and stimulants on the cerebellar evoked potentials. In particular, chlorpromazine (CPZ) significantly increased the potentials evoked by the electrical stimulation of the periphery in the cerebellar cortex, and it was clear that this drug showed different actions in the different areas of the cerebellar cortex. Furthermore, we investigated the CPZ-induced enhancement of cerebellar evoked potentials by microinjection of CPZ, norepinephrine (NE), or dopamine (DA) into the pre-cerebellar nuclei, such as the nucleus reticularis lateralis (LRN) and nucleus olivaris inferior, using the intact, decerebrated, or spinal cat. Our results suggest that the intravenous CPZ-induced enhancement of the cerebellar potentials may be due to depression of the noradrenergic system (2-4) from the LRN to the spinal cord, the so-called descending inhibitory mechanism, resulting from CPZ-induced blockade of DA receptors in the LRN (5).

With regard to the innervation from the LRN to the spinal cord, there are many reports (6-9). Pertaining to a functional role of the LRN, Hall et al. (2) demonstrated that the tonic descending inhibition of spinal dorsal horn neurons was reduced significantly following bilateral lesions in the LRN and demonstrated that lateral reticular areas may have a functional role in the control of pain. Morton et al. (3) proposed that the tonic descending inhibition of dorsal horn nociceptive neurons in the cat is mediated by the LRN. Ossipov and Gebhart (4) reported that an α2-adrenoceptor in the LRN apparently mediates a disinhibition of nociceptive transmission,
likely by removal of tonic descending influences. Thus, the LRN plays a significant role in the control mechanism of inputs from the periphery, not only as a pre-cerebellar nucleus from the periphery to the cerebellum (10, 11), but also as the cell body of noradrenergic descending neurons to the spinal cord.

In general, it is said that CPZ blocks not only DA receptors but NE adrenoceptors (12). Iversen (13) and Clement-Cormier et al. (14) reported that CPZ had strong blocking actions on catecholamine-like receptors at the synaptic level. Kashiba (15) demonstrated that daily administration of CPZ for over 20 days resulted in degenerative changes of the noradrenaline terminals. Furthermore, in our previous studies (5), microinjection of NE (lower dose) into the LRN significantly depressed the cerebellar potentials evoked by the electrical stimuli of the periphery, in a manner similar to DA-induced change. Thus, we think that the interaction between CPZ-induced enhancement of the cerebellar evoked potentials and NE adrenoceptors in the LRN may be significant.

In the present work, we investigated CPZ-induced enhancement of cerebellar potentials evoked by the peripheral nerve stimulation with regard to \( \alpha_1 \) and \( \alpha_2 \)-adrenoceptors in the LRN using several adrenergic agents.

### Materials and Methods

Forty-two adult cats of either sex, weighing 2.6–3.4 kg, were used. The animals were anesthetized initially with ether and then fixed on a stereotaxic instrument (Narishige type). Tracheal, arterial and venous cannulas were inserted. After the recovered from ether anesthesia, the animals were artificially ventilated (25 revolutions per minute) following an intravenous injection of gallamine triethiodide. Xylocaine spray was frequently applied to the entire surgical area throughout the entire experiment. End-tidal CO\(_2\) was maintained within physiological limits. Body temperature, monitored by a rectal probe, was maintained at 37–38°C by means of a heating pad. Arterial blood pressure, electrocardiogram (II lead), and \( O_2 \) saturation were recorded throughout the experiment.

The ipsilateral superficial radial nerve (SR) of the forelimb against the recording site was dissected and cut at its peripheral end. The central part of the nerve end was placed on a bipolar stimulating electrode (platinum wires) with a 2 mm polar separation and stimulated in a pool of warm liquid paraffin to prevent drying and then kept between 37–38°C. A single rectangular pulse (duration: 0.1–0.2 msec, intensity: 3–4 V) was applied at a rate of 1 trial per 5 sec.

To record the potentials evoked in the cerebellar cortex, part of the occipital bone against the recording site was removed to expose the vermis, which was then immersed in a pool of warm liquid paraffin. Recordings were made from the vermis using a monopolar platinum ball electrode (diameter of 0.3 mm).

A stainless steel concentric electrode with a diameter of 0.6 mm (tip separation of 0.5 mm) was inserted stereotaxically to stimulate at high frequency the ipsilateral LC (P, 2.0; L, 2.0; H, -2.0) against the recording site and the LRN, located according to the atlas of Snider and Niemer (16). As the electrical stimulation at high frequency, a single rectangular pulse of 100 \( \mu \)sec duration, 300 \( \mu \)A intensity, and 100 Hz frequency was applied to stimulate the LC for 1–2 min.

A stainless steel concentric electrode that contained the drug-microinjecting cannula (type: E-7006, MT Giken) with a diameter of 0.6 mm was inserted stereotaxically to stimulate electrically the LRN. A single rectangular pulse (duration: 100–200 \( \mu \)sec, intensity: 3–4 V) was applied at a rate of 1 trial per 5 sec. Each drug was administered in volumes of 0.5–1.0 \( \mu l \) via the drug-microinjecting cannula. The reference electrode was located on the temporal muscle.

On termination of the experiment, the brain was removed and fixed in 10% formalin and then sectioned serially at 50 \( \mu m \) to verify histologically the point of electrode insertion and microinjecting cannula.

In the above experiments, a stimulator (Model 3F46, San-ei) was used for SR, LC and LRN stimulations. The evoked potentials that were obtained by 10 repetitive stimuli were averaged by a signal processor (Model
7T07) via a dual beam oscilloscope, and these recordings were made on an X-Y recorder (Model WX 442, Watanabe). The upper side of evoked potentials was expressed as a negative potential and the lower side, as a positive one.

The amplitudes of evoked potentials were measured from the baseline to the peak of a negative or positive wave. The time from the stimuli to the peak of negative or positive component was termed as the peak time.

The drugs used in these experiments were chlorpromazine HCl (Shionogi), dl-noradrenaline (Nacalai Tesque, Ltd.), prazosin HCl (Tokyo Chemical Industry Co., Ltd.), clonidine HCl (Sigma), yohimbine HCl (Nacalai Tesque, Ltd.), and L-phenylephrine HCl (Tokyo Chemical Industry Co., Ltd.), which were dissolved in physiological saline solution. Prazosin HCl was dissolved in dimethyl sulfoxide.

The statistical significance of the data obtained was assessed using the two-tailed Student's t-test.

Results

I. Electrical stimulation at high frequency of the ipsilateral LC: The electrical stimulation of the superficial radial nerve produced potentials consisting of negative and positive components, which had peak times of 23.4±2.9 msec and 45.2±2.4 msec in the cerebellar cortex. We examined the effects of several drugs on the amplitude of these components in the following experiments.

In order to investigate the connection from the LC, which contains the noradrenergic cell body, to the ipsilateral LRN, the LC was electrically stimulated at high frequency. Electrical stimuli at high frequency of the ipsilateral LC enhanced both amplitudes of cerebellar potentials evoked by the SR stimulation, by 22–23%, immediately after or during high frequency stimulation (Fig. 1, N=12). These increases of cerebellar potentials during a conditioning period were stronger than those immediately after this stimulation.

Even after pretreatment of an α2-adrenoceptor antagonist, yohimbine (5 μg, N=6), electrical stimulation at high frequency of the LC increased both components of cerebellar potentials by 16–24% (Fig. 2, left). However, similar stimulation hardly changed cerebellar potentials by pretreatment with an α1-adrenoceptor antagonist, prazosin (5 μg, N=5) (Fig. 2, right).

Fig. 1. Effects of an electrical stimulation at high frequencies of ipsilateral locus coeruleus (LC-HFS) on cerebellar potentials evoked by the peripheral nerve stimulation. Right responses indicate the actual cerebellar potentials evoked by the superficial radial nerve stimulation. The control value (before treatment) is shown as 100%. N: negative component, P: positive one. **P<0.01.
Fig. 2. Effects of an electrical stimulation at high frequencies of ipsilateral locus coeruleus after pretreatment with yohimbine microinjected (5 μg, left) or prazosin (5 μg, right) into the nucleus reticularis lateralis on cerebellar potentials evoked by the peripheral nerve stimulation. The control value (before treatment) is shown as 100%. N: negative component, P: positive component. **P<0.01.

Fig. 3. Effects of microinjection of norepinephrine (NE: 10 and 30 μg) into the nucleus reticularis lateralis on cerebellar potentials evoked by the peripheral nerve stimulation. The control value (before treatment) is shown as 100%. –○–: negative component, –●–: positive one. *P<0.05, **P<0.01.

II. Effects of NE (10–30 μg) into the ipsilateral LRN on the cerebellar potentials evoked by the electrical stimulation of SR: Microinjection of NE (10 μg, N=7) into the ipsilateral LRN decreased the amplitude of two components of the cerebellar potentials by 10–14% at 10–15 min (Fig. 3, left). On the other hand, NE (20 μg) decreased them by 11–12% in 6 out of 13 animals; and in 7 out of 13 animals, this drug increased them by 10–19%. Thirty micrograms (N=5) of NE increased them significantly by 18–25% (Fig. 3, right). Thus, a lower dose of NE decreased the amplitude of cerebellar potentials, and higher doses of this drug increased them.

III. Effects of clonidine microinjected and pretreatment with CPZ into the LRN on cerebellar potentials: In order to investigate whether or not CPZ-induced enhancement of inputs from the periphery to the cerebellar...
cortex is due to CPZ-induced blockage of an $\alpha_2$-adrenoceptor in the LRN, we used an $\alpha_2$-adrenoceptor agonist, clonidine, and pretreatment with CPZ in the following experiment.

Microinjection of clonidine (5 $\mu$g, N=10) into the LRN significantly depressed amplitudes of both components of cerebellar potentials evoked by SR stimulation by 13-16% at 10-30 min (Fig. 4). Recovery was observed to occur at 50-60 min. When clonidine-induced depression was obviously recognized, the cerebellar potentials produced by the electrical stimulation of the ipsilateral LRN increased by 20-30% (Fig. 4). On the other hand, clonidine-induced decrease of cerebellar potentials was obviously antagonized by pretreatment with CPZ (2-4 $\mu$g, N=5) before 5 min (Fig. 4).

IV. Effects of phenylephrine microinjected or pretreatment with CPZ into the LRN on cerebellar potentials: Next, we used an $\alpha_1$-adrenoceptor agonist, phenylephrine, in the following study. Microinjection of phenylephrine (10 $\mu$g, N=10) into the LRN increased significantly amplitudes of both components of cerebellar potentials produced by SR stimulation by 18-20% at 15-30 min (Fig. 5, right). Phenylephrine-induced enhancement of cerebellar potentials was antagonized by pretreatment with an $\alpha_1$-adrenoceptor antagonist, prazosin (5 $\mu$g, N=8). Furthermore, pretreatment of prazosin decreased cerebellar potentials produced by SR stimulation by 8-10%, but this decrease was not significant. On the other hand, pretreatment with CPZ (1 $\mu$g, N=11) did not change the phenylephrine-induced enhancement (Fig. 5, left).

All data from our present experiments are shown in Table 1.

Discussion

In the present work, we studied CPZ-induced enhancement of the cerebellar potential with regard to $\alpha_1$- and $\alpha_2$-adrenoceptors in the LRN using several adrenergic agents. Palkovits and Jacobowitz (17) demonstrated that cell bodies which contain NE are present in the LRN. Ossipov and Gebhart (4) reported that an $\alpha_2$-adrenoceptor in the LRN...
Fig. 5. Effects of microinjected phenylephrine (Phe: 10 μg) and phenylephrine after pretreatment with chlorpromazine (CPZ) into the nucleus reticularis lateralis on cerebellar potentials evoked by peripheral stimulation. The effects of Phe after pretreatment with CPZ on cerebellar potentials are shown on the left. The control value (before treatment) is shown as 100%. -○--; negative component, —●—; positive one. *P<0.05, **P<0.01. The histograms on the right indicate effects of Phe alone, Phe after pretreatment with CPZ, and Phe after pretreatment with prazosin (5 μg) on cerebellar potentials. The control value (before treatment) is shown as 100%. N: negative component, P: positive one. *P<0.05, **P<0.01.

Table 1. Effects of several drugs microinjected into the nucleus reticularis lateralis on the cerebellar potential evoked by the electrical stimulation of the ipsilateral superficial radial nerve

| Test substance (Dose) | No. of cats | Change |
|-----------------------|-------------|--------|
| I. 1. Ipsilateral locus coeruleus high frequency stimulation (LC-HFS) | 12 | 22–23% ↑ ** |
| 2. Yohimbine (5 μg)+LC-HFS | 6 | 16–24% ↑ ** |
| 3. Prazosin (5 μg)+LC-HFS | 5 | No change |
| II. 1. Norepinephrine (10 μg) | 7 | 10–14% ↓ * |
| 2. Norepinephrine (20 μg) | 6 | 11–12% ↓ * |
| 3. Norepinephrine (30 μg) | 7 | 10–19% ↑ * |
| III. 1. Clonidine (5 μg) | 10 | 13–16% ↓ ** |
| 2. Chlorpromazine (2–4 μg) + clonidine (5 μg) | 5 | Antagonization |
| IV. 1. Phenylephrine (10 μg) | 10 | 18–20% ↑ ** |
| 2. Prazosin (5 μg) + phenylephrine (10 μg) | 8 | Antagonization or 8–10% ↓ |
| 3. Chlorpromazine (1 μg) + phenylephrine (10 μg) | 11 | 17–21% ↑ ** |

↑: Increasing action, ↓: Decreasing action. *P<0.05, **P<0.01.
apparently mediates a disinhibition of nociceptive transmission. Furthermore, Cahusac and Hill (18) suggested the existence of \( \alpha_2 \)-receptors in the LRN. In the previous results (5), as microinjection of NE into the LRN influenced the cerebellar potentials, we thought that NE receptors were present in the LRN, while Janss and Gebhart (19) reported that the LRN receives projections of the noradrenergic system from the LC, which contains the NE cell body. Therefore, we firstly examined the electrical stimulation of the LC at high frequencies. The electrical stimulation of the LC during a conditioning period increased the cerebellar potentials evoked by the peripheral nerve stimulation. Although enhancements of cerebellar potentials following the electrical stimulation of the LC were not recognized by pretreatment with microinjection of an \( \alpha_1 \)-adrenoceptor antagonist, prazosin, similar stimulation increased them after pretreatment with microinjection of the \( \alpha_2 \)-adrenoceptor antagonist yohimbine. The fact that significant increase of cerebellar potentials was recognized by electrical stimulation of the LC at high frequencies shows that NE that was released from noradrenergic terminals of the LC binds on an \( \alpha_1 \)-adrenoceptor in the LRN, and consequently, the activity of the LRN was depressed. Therefore, it was suggested that CPZ-induced enhancement of cerebellar potentials evoked by the peripheral nerve stimulus was due to disinhibition of the descending inhibitory system the LRN.

We also investigated subtypes of adrenoceptors within the LRN. Microinjection of NE (10 \( \mu \)g) into the LRN decreased cerebellar potentials from the periphery; and conversely, 20–30 \( \mu \)g of NE increased them. Basile and Dunwiddie (20) reported that excitations of Purkinje neurons in in vitro rat cerebellar slices were evoked by low concentrations of NE (0.5–1.0 \( \mu \)M), and perfusion with higher concentration of NE (>16 \( \mu \)M) caused a depression of Purkinje neuron activity. Kow and Pfaff (21) reported that the inhibitory response could be evoked at doses lower than those required to evoke the excitatory response in experiments with varying doses of NE and furthermore showed that the opposite excitatory and inhibitory responses were found to be mediated by different types of adrenergic receptors. Pang and Rose (22) demonstrated that the NE-induced inhibitory response of hippocampal complex-spike neurons was mediated by an \( \alpha_1 \)-receptor. Although an inhibitory action via \( \alpha_1 \)-receptors has not been shown in the LRN, the present results indicate that this action may act on \( \alpha_2 \)-adrenoceptors of the LRN at the postsynaptic level. Taken together, we thought that lower doses of microinjected NE bound to \( \alpha_2 \)-autoreceptors of the noradrenergic terminal from the LC and blocked the release of NE as a neurotransmitter from a noradrenergic terminal of the LC. As the result, activities of the LRN itself may be enhanced, and the descending inhibitory adrenergic system from the LRN depressed the cerebellar potentials evoked by peripheral stimulation. On the other hand, it was also thought that higher doses of microinjected NE combine with \( \alpha_1 \)-adrenoceptors within the LRN, and then the activities of the LRN itself may be functionally depressed and cerebellar potentials evoked by the peripheral stimuli increased.

Sagen and Proudfit (23) demonstrated that \( \alpha_1 \)- and \( \alpha_2 \)-adrenoceptors exist in the postsynapse and presynapse, respectively, in adrenergic terminals of the nucleus raphe magnus, and the \( \alpha_2 \)-adrenoceptor was the autoreceptor of NE as a neurotransmitter. Furthermore, they also showed that phenylephrine and prazosin acted as an agonist and an antagonist of \( \alpha_1 \)-adrenoceptors, respectively. Clonidine and yohimbine acted as an agonist and an antagonist of \( \alpha_2 \)-adrenoceptors, respectively. Thus, we hypothesized that CPZ blocks \( \alpha_2 \)-autoreceptors in adrenergic terminals from the LC rather than \( \alpha_1 \)-adrenoceptors within the LRN. As a result, NE that was released from LC terminals may act at \( \alpha_1 \)-adrenoceptors on the LRN, and it may attenuate activities of the LRN. Therefore, CPZ-induced enhancement of cerebellar potentials may be due to the depression of the
descending inhibitory adrenergic system.

Accordingly, we observed the effects of the $\alpha_2$-agonist clonidine and the $\alpha_1$-agonist phenylephrine. Microinjection of clonidine into the LRN significantly decreased the cerebellar potentials evoked by the peripheral stimuli. To examine whether microinjected clonidine attenuates the NE release from LC terminals and if the activities of the LRN are enhanced, we investigated the cerebellar potential evoked by the electrical stimulation of the LRN. When microinjected clonidine significantly decreased the cerebellar potential, the potential evoked by the LRN stimulation on the cerebellar cortex was obviously enhanced. Thus, we thought that microinjected clonidine attenuates the NE release from LC terminals and the activities of the LRN may be enhanced as the result of clonidine-induced stimulation of $\alpha_2$-autoreceptors of the adrenergic neurons from the LC. Furthermore, after pretreatment with CPZ, microinjection of clonidine did not change the cerebellar potential evoked by peripheral stimulation. It was suggested that because clonidine was an $\alpha_2$-agonist, CPZ may block $\alpha_2$-autoreceptors of the adrenergic terminal from the LC. On the other hand, microinjection of phenylephrine increased cerebellar potentials from the periphery. Although pretreatment of CPZ did not influence the phenylephrine-induced increase, pretreatment by the $\alpha_1$-receptor antagonist prazosin significantly antagonized phenylephrine-induced change. It was suggested that CPZ hardly blocks $\alpha_1$-adrenoceptors on the LRN itself.

Therefore, our previous hypotheses were supported by the present results. Namely, intravenous and microinjected CPZ blocks not only DA receptors of the LRN but also $\alpha_2$-autoreceptors in the adrenergic terminal from the LC rather than $\alpha_1$-adrenoceptors within the LRN. As a result, NE that was released from LC terminals may act on $\alpha_1$-adrenoceptors in the LRN and may attenuate the activities of the LRN. Therefore, it is clear that CPZ-induced enhancement of cerebellar potentials evoked by peripheral nerve stimulation may be due to the depression of the descending inhibitory adrenergic system.

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