Putative Feed-Forward Control of Jaw-Closing Muscle Activity During Rhythmic Jaw Movements in the Anesthetized Rabbit

AKIRA KOMURO, TOSHIFUMI MORIMOTO, KOICHI IWATA, TOMIO INOUE, YUJI MASUDA, TAKAFUMI KATO, AND OSAMU HIDAKA

1Department of Oral Physiology and 2Department of Orthodontics and Dentofacial Orthopedics, Graduate School of Dentistry, Osaka University, Osaka 565-0871, Japan

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Komuro, Akira, Toshifumi Morimoto, Koichi Iwata, Tomio Inoue, Yuji Masuda, Takafumi Kato, and Osamu Hidaka. Putative feed-forward control of jaw-closing muscle activity during rhythmic jaw movements in the anesthetized rabbit. J Neurophysiol 86: 2834–2844, 2001. When a thin plastic test strip of various hardness is placed between the upper and lower teeth during rhythmic jaw movements induced by electrical stimulation of the cortical masticatory area (CMA) in anesthetized rabbits, electromyographic (EMG) activity of the masseter muscle is facilitated in a hardness-dependent manner. This facilitatory masseteric response (FMR) often occurred prior to contact of the teeth to the strip, and thus preceded the onset of the masticatory force. Since this finding suggests involvement of a feed-forward mechanism in the induction of the FMR, the temporal relationship between the onset of the FMR and that of the masticatory force was analyzed in five sequential masticatory cycles after application of the strip. The FMR was found to precede the onset of masticatory force from the second masticatory cycle after application of the strip, but never did in the first cycle. This finding supports the concept of a feed-forward control mechanism that modulates FMR timing. Furthermore, the FMR preceding the force onset disappeared after making a lesion of the mesencephalic trigeminal nucleus (MsV) where the ganglion cells of the muscle spindle afferents from the jaw-closing muscles are located. In contrast, no such change occurred after blocking periodontal afferents by transection of both the maxillary and the inferior alveolar nerves. The putative feed-forward control of the FMR is therefore dependent mainly on sensory inputs from the muscle spindles, but little on those from the periodontal receptors, if any. We further examined the involvement of the CMA with the putative feed-forward control of the FMR via the transcortical loop. For this purpose, rhythmic jaw movements were induced by stimulation of the pyramidal tract. No significant change in the timing of the FMR occurred after the CMA ablation, which strongly suggests that the CMA is not involved in the putative feed-forward control of the FMR. The FMR was also noted to increase significantly in a hardness-dependent manner even after the MsV lesion, although the rate of increment decreased significantly. Contribution of muscle spindles and periodontal receptors to the hardness-dependent change of the FMR is discussed.

Introduction

Electrical stimulation to the cerebral cortical masticatory area (CMA) in rabbits induces rhythmic jaw movements that resemble natural mastication (Bremer 1923). When a small steel ball or a thin plastic strip is placed between the upper and lower teeth during cortically induced rhythmic jaw movements (CJM) in the anesthetized rabbit, the masseteric electromyographic (EMG) bursts are facilitated (Lavigne et al. 1987; Liu et al. 1993; Morimoto et al. 1989). Recording the masticatory force in similar experiments, Hidaka et al. (1997) found that the force increased with the hardness of the chewing strips, simultaneously with facilitation of the masseteric EMG. They proposed that the sensory feedback from muscle spindles in the jaw-closing muscles via the jaw-jerk reflex arc is primarily responsible for the hardness-dependent modulation of the facilitatory masseteric response (FMR).

Hidaka et al. (1997) also noted that the FMR often preceded the onset of the masticatory force. In other words, the FMR occurred prior to contact of the teeth with the chewed substance. This finding is not explained by a simple feedback mechanism, but suggests involvement of a feed-forward mechanism. Although sensory feedback via the reflex arc has an important role in the modulation of muscle activity during voluntary movements, the delays in most reflex arcs are large, making feedback control too slow to account for rapid movement. The concept of feed-forward control has been accepted as the mechanism for rapid and smooth, in which the consequences of movements that are preprogrammed using previous sensory information (Blakemore et al. 1998; Wolpert 1997; Wolpert et al. 1995).

As for human mastication, Ottenhoff et al. (1992a,b, 1993) found that when food-simulating force was given to the mandible using a computer-controlled device while subjects were making rhythmical open-close jaw movements, an additional muscle activity (AMA) was induced in the masseter muscle in addition to the muscle activity required for the basic rhythmical movements of the jaw. This AMA appeared before the onset of the force from the second cycle with force, while it did not appear in the first cycle with force. The AMA is regarded as the muscle activity that is made in preparation for anticipated force. The authors proposed that an open-loop (feed-forward) mechanism is responsible for the control of the AMA, in which sensory information about the bolus size in the previous masticatory cycles might affect the onset of the AMA in the following masticatory cycles.

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Sensory information associated with previous action is therefore important for the feed-forward control of the subsequent movements. However, the kinds of sensory receptors those are responsible for the feed-forward control of mastication has not been fully evaluated. If the FMR in the rabbits is proved to be similar in physiologic nature to the AMA in humans, it may be concluded that the feed-forward mechanism is fundamentally involved in the control of masticatory jaw movements, regardless of the kind of animal. Also, the putative feed-forward phenomenon in the rabbits is available to identify the sensory receptors responsible for this type of control of masticatory jaw movements by blocking sensations arising from the oral-facial region.

The first aim of the present study was to examine whether the FMR in rabbits is similar in physiologic nature to the AMA in humans, by analyzing the temporal relationship between the onset of the FMR and that of the masticatory force on the first five masticatory cycles after chewing the strip. The second aim was to identify the sensory receptors responsible for the putative feed-forward control of the FMR by blocking sensations arising from the oral-facial region.

As described above, the putative feed-forward phenomenon of the rabbit was induced under anesthetic state (Hidaka et al. 1997) and thus without concern of consciousness. This fact, however, does not necessarily deny the possibility that the cerebral cortex contributes to this phenomenon via a transcortical loop. In the third aim, we analyzed the effects of CMA ablation on the putative feed-forward phenomenon to examine the validity of this possibility.

METHODS

Surgical procedures

The surgical procedures were nearly identical to those described previously (Hidaka et al. 1997). They were reviewed and approved by the Osaka University Faculty of Dentistry Intramural Animal Care and Use Committee. Twenty-five male rabbits weighing 2.5–3.5 kg were used in this study, where nine rabbits were used as controls. In 11 rabbits, we studied the effects of trigeminal sensory deprivation on the putative feed-forward phenomenon. The remaining five rabbits were used to examine the effects of CMA ablation on this phenomenon. Each rabbit was initially anesthetized with intravenous administration of ketamine HCl (Ketalar 10, Sankyo, 16 mg/kg) and sodium thiopental (Isozol, Yoshitomi, 20 mg/kg) via an ear vein. After tracheal cannulation, anesthesia was maintained with a mixture of halothane (1.5–2.0%) and oxygen during surgery at such a level that neither an apparent corneal reflex nor spontaneous eye movement was present. The heart rate was continuously monitored and maintained in the range between 210 and 240 beats/min. A photo-diode was attached to the mentum to monitor jaw movements by means of a charge-coupled device (CCD) camera (C-2399, Hamamatsu Photonics, Hamamatsu, Japan). Enamel-coated copper wire electrodes were inserted into the left masseteric and digastric muscles to record EMG activity. A small force-displacement transducer (length 6 mm, width 4 mm, height 4 mm), which was developed at our department (Ogata et al. 1993), was fixed at the left lower molar region to detect the timing of the test strip application (the onset of the force production). To fix the transducer, the facial skin was incised from the corner of the mouth to the molar region. After the crowns of the lower first and second molars were ground, the transducer was fixed to the ground surface with self-curing resin. The upper surface of the transducer was fixed to align with the occlusal surface of the remaining molars (Fig. 1), so that the occlusal height did not change. All wound margins were anesthetized using small injections of xylocaine hydrochloride (Xylocaine, Fujisawa). According to the method described previously (Sawyer et al. 1954), the head of the rabbit was fixed to a stereotaxic apparatus by means of three skull screws in such a position that lambda was 1.5 mm below bregma (Sawyer et al. 1954).

Cortical stimulation and intraoral stimulation

For electrical stimulation of the cortical masticatory area (CMA), the cortical surface was exposed between 1 and 7 mm anterior from bregma and mediolaterally between 3 mm lateral to the midline and the lateral edge of the cranium. Glass-coated metal microelectrodes (1–2 MΩ at 1 kHz) were used for the intracortical microstimulation. Square pulses (30 Hz, duration 0.2 ms, <0.1 mA) were delivered to evoke CRJMs. Five test strips of the same size (2.5 mm thick, 5 mm wide, 15 mm long), but of different hardness (relative hardness: 27, 47, 67, 84, and 91), were prepared. The strips were placed in a random order between the upper left molar and the upper surface of the transducer during CRJMs. The strips were numbered from 1 to 5, according to an increasing order of the hardness. In the experiments examining the effects of the trigeminal sensory deprivation on the putative feed-forward phenomenon, no. 3 strips were applied.

Data analysis

Data on the masseteric EMG, masticatory force, and jaw movements were digitized at 2 kHz, 2 kHz, and 600 Hz, respectively. These data were fed into a personal computer (Dell Optiplex XMT 5133, Dell Computer, Round Rock, TX) and analyzed using Spike2 software (Cambridge Electronic Design, Cambridge, UK). The EMG data were first software-rectified and smoothed by a low-pass Finite Impulse Response filter at a cutoff frequency of 50 Hz. Then the magnitude and onset of the FMR and the onset of the masticatory force were analyzed using the procedures described in RESULTS. If the FMR is produced simply via the pathway of the jaw-jerk reflex, its latency that measured as the time interval between the FMR onset and the force onset, must be longer than the shortest latency for the jaw-jerk reflex, i.e., 6 ms (Hidaka et al. 1997). On the contrary, when the latency is shorter than 6 ms, the FMR is considered induced in a feed-forward manner.

Evaluation of sensory inputs responsible for the temporal control of masseteric activity

We examined the effects of deprivation of the sensory inputs from the jaw muscle spindles and the periodontal receptors on the FMR in 11 rabbits. These rabbits were divided into two groups, based on the...
kind of surgical operations executed. In one group, composed of five rabbits, the maxillary and inferior alveolar nerves were cut on the left side to block sensory inputs from the periodontal receptors. Since the lower dental arch of the rabbits is far smaller than the upper one, the lower teeth occluded only the ipsilateral upper teeth during chewing the strip. The unilateral denervation thus sufficiently blocks sensory inputs from the periodontal receptors during chewing. The maxillary nerve was exposed at the bottom of the orbit after incision of the skin along the upper border of the zygomatic arch. The inferior alveolar nerve was exposed in the mandibular canal, after grinding of the overlying bone, and then cut close to the mandibular foramen. Adequate elimination of the periodontal sensation was confirmed by the following two procedures: 1) the threshold of the jaw-opening reflex induced by electrical stimulation applied to the periodontal structures of the molars through fine needle electrodes, increased more than 10 times after the denervation; and 2) complete transection of the maxillary and inferior alveolar nerves were identified under microscopic observation after the experiments.

In the other group of six rabbits, an electric lesion in the MesV was performed to block sensory inputs from the muscle spindles of the jaw-closing muscles. Glass-coated metal microelectrodes (1–2 MΩ at 1 kHz) were used for locating and making lesion of the MesV. For insertion of the microelectrodes, the cortical surface was exposed, centered at 14 mm posterior to bregma and 2 mm left of the midline. The MesV neurons were first located electrophysiologically by recording multiunit activities responding to passive jaw opening and then coagulated thermally by passing DC currents through the electrode (40 μA, 40 s).

The degree of the MesV lesion was estimated by the decrease in the magnitude of the stretch reflex response in the masseter muscle that was elicited by a 1-mm depression of the mandible using a mechanical stretcher. The lesions in the MesV were histologically investigated later. For this purpose, the rabbits were deeply anesthetized and perfused with saline through the ascending aorta, followed by 10% formaldehyde.

Ablation of CMA

To determine whether the temporal control of the FMR relies on the transcortical loop, the effects of CMA ablation were examined in five rabbits. For this purpose, rhythmic jaw movements were induced by stimulation of the pyramidal tract applied 3 mm posterior to bregma. The parameters for electrical stimulation of the pyramidal tract were the same as those applied for stimulation of the CMA. The ablation was performed unilaterally in the region corresponding to the area exposed for electrical stimulation, that sufficiently includes the CMA reported by Liu et al. (1993), i.e., the region enclosed mediolaterally between 6.5 and 8.5 mm from the midline and anteroposteriorly between 2 and 6 mm anterior from bregma. The onset of the FMR and that of the force production were compared before and after the CMA ablation.

Statistical analysis

The data are presented as the means ± SD. The difference between the two factors (test strip hardness and presence of a MesV lesion) was tested by two-way ANOVA. Paired t-tests were performed for comparison of the data before and after denervation of the trigeminal branches, before and after the MesV lesion and also before and after the CMA ablation. The level of P < 0.05 was considered to be significant.

RESULTS

Timing of masseteric EMG activity in relation to a masticatory cycle

An example of the effects of strip application on the masticatory force, masseteric EMG activity, and jaw movements during CRJMs in a control rabbit is shown in Fig. 2A. Among the various types of CRJMs, crescent-shaped jaw movements were chosen for analysis of the timing of the masseteric EMG activity in relation to a masticatory cycle, because this type of movements most resembles the jaw movements during natural molar chewing (Liu et al. 1993; Lund et al. 1984). The jaw movement cycles before and during strip application were designated as control and experimental cycles, respectively. In the control cycles, a small force was produced by contact of the transducer with the upper molars. In the experimental cycles, the force increased simultaneously with an increase in the masseteric EMG activity and its duration due to strip application, which confirms the results of a previous study (Hidaka et al. 1997).

To compare the timing of the EMG activity of the control cycles with that of the EMG activity of the experimental cycles, the masticatory force, masseteric EMG activity and jaw movements of five control (I in Fig. 2A) and five experimental cycles (II in Fig. 2A) were averaged by triggering the traces at the point of maximum jaw opening. The thin and thick waveforms in the top three traces of Fig. 2B are the data from the control and experimental cycles, respectively. The difference in the averaged EMG data between these two types of cycles was regarded as the FMR, which is shown at the bottom of Fig. 2B. To examine the temporal relationship between the onset of the FMR and that of the masticatory force, both onsets were first assessed as follows. The mean and standard deviation (SD) of the masticatory force during 1/10 of the total cycle length (TCL: the interval between 2 consecutive maximum jaw openings) from the maximum jaw opening were calculated on 5 experimental cycles. The onset of the masticatory force (dotted vertical lines with open triangles in Fig. 2, B and C) was defined as the moment when the force level exceeded the mean ± 2 SD. To determine the onset of the FMR, the SD of the EMG activity of the five control cycles during the period from the maximum jaw opening to 10 ms after the force onset was calculated with each bin analyzed at 2 kHz. Twice the largest SD was determined as the threshold, and the moment when the FMR first exceeded the threshold was considered the onset of the FMR (thin vertical lines with solid triangles in Fig. 2, B and C). In the example shown in Fig. 2, the onset of the FMR preceded the force onset by 18.3 ms, which means that the FMR started before the strip was actually bitten between the upper teeth and the transducer.

We also noted that at the first cycle after the strip was removed, the FMR onset still preceded the force onset, although the FMR was greatly decreased (Fig. 2A), which is similar to the finding reported by Ottenhoff et al. (1992a). This phenomenon also suggests concern of the feed-forward control of CRJMs, but we did not further analyze it in the present study.

Analysis on the FMR onset in the first five experimental cycles

Since the above finding suggests that the FMR could be controlled in a feed-forward manner, we next analyzed the relationship between the FMR onset and the force onset on the first five experimental cycles, keeping aware that the onset of the FMR must precede the force onset on the second and
subsequent experimental cycles, but not on the first cycle, as described in the INTRODUCTION. On the first experimental cycle (E1 in Fig. 3), the onset of the FMR (the thin vertical lines with solid triangles) delayed the force onset (dotted lines with open triangles) by about 20 ms. In the subsequent four experimental cycles (E2 to E5 in Fig. 3), however, the onset of the FMR preceded the force onset by about 15 ms on average. The reversal of the relationship between the onset of the FMR (solid triangles in Fig. 3B) and that of the masticatory force (open triangles in Fig. 3B) from the second experimental cycles is also demonstrated on the jaw movement traces on the frontal plane (Fig. 3B).

FIG. 2. Determination of the onset of facilitatory masseteric response (FMR). A: an example of the recordings of the masticatory force, masseteric EMG and jaw movement during cortically induced rhythmic jaw movements (CRJMs). Force, masticatory force; Mass, masseteric EMG activity; Ver and Hor, vertical and horizontal components of the jaw movements, respectively. The bottom traces show jaw movements on the frontal plane during the control (I) and experimental cycles (II). B: the averaged and superposed data of masticatory force, masseteric EMG and vertical jaw movements during 5 control and 5 experimental cycles, aligned at the point of maximum jaw opening. Thick lines, experimental cycle; thin lines, control cycle; FMR, difference in the rectified and averaged EMG data between the experimental and control cycles. The thin vertical solid lines with solid triangle indicate the onset of the FMR. The vertical dotted lines with open triangle indicate the force onset in the experimental cycle. Note that the onset of the FMR precedes the force onset. C: the same records as B, but on an expanded scale. The horizontal dotted line indicates the threshold of the FMR. Other signs are the same as those in B.

The results obtained from 20 control rabbits are graphically shown in Fig. 4A (●). The difference in the relationship between the control and experimental cycles was examined by one-way ANOVA, which was followed by post hoc Scheffe’s F-test (multiple comparisons) when justified. The results are summarized in Table 1. The FMR was elicited at $44.9 \pm 15.3$ ms ($\text{mean} \pm \text{SD}; n = 20$) after the onset of the force production in E1. In E2 to E5, however, the onset of the FMR preceded the force onset by $14.6 \pm 8.8$ ms, and there were no significant differences between the four cycles (Fig. 4A). Temporal relationship between the FMR and the masticatory force thus reversed between E1 and E2.
Analysis of the magnitude of horizontal jaw movements in the first five experimental cycles

As stated above, the FMR appeared earlier in E2 to E5 than in E1. To examine how the difference in the onset of the FMR is reflected on the jaw movements, their patterns were compared between cycle E1 and cycles E2 to E5. It was apparent that the horizontal movement of the cycles E2 to E5 was greater than that of the cycle E1 (Fig. 3B). The magnitude of the movement was analyzed and is graphically shown in Fig. 4B. The horizontal movement was 5.32 ± 2.25 mm for E1, and 6.89 ± 2.47 mm for E2 to E5, the former being significantly smaller than the latter. In contrast, there were no significant differences in the horizontal jaw movements between cycles E2 and E5. The early onset of the FMR may serve to develop the horizontal jaw movement of a masticatory cycle.

Effects of sectioning the maxillary and inferior alveolar nerves

To examine the contribution of periodontal sensation on the putative feed-forward control of the FMR, the effects of transection of the maxillary and inferior alveolar nerves on the masticatory force, masseteric EMG activity, and jaw movements were evaluated in the same rabbits as shown in Fig. 2A (Fig. 5A). The temporal relationship between the masticatory force and the FMR did not significantly change after denervation as shown in Fig. 5B. Summated results obtained from five
Effects of lesioning the MesV

When the MesV was lesioned, an ipsilateral masseteric response through the jaw-jerk reflex pathway elicited by depressing the mandible greatly decreased, while the contralateral response remained unaffected. As previously reported (Morimoto et al. 1989), the MesV lesion reduced the masticatory force and the masseteric EMG during chewing of the strip.

The temporal relationship between the FMR onset and the force onset was compared before and after the MesV lesion. An example is shown in Fig. 6. The force appeared at 44.0 ms after the maximum jaw opening both before and after the MesV lesion. In contrast, the onset of the FMR preceded the force onset by 20.5 ms before the MesV lesion, while it delayed the force onset by 51.6 ms after the MesV lesion in which the minus sign indicates that the FMR onset preceded the force onset. Table 2 shows the summary of the results obtained from six rabbits with the MesV lesion. No significant difference was recognized before and after the MesV lesion in the temporal relationship between the period of maximum jaw opening and the force onset (45.1 \(\pm 1.7\) ms, before the MesV lesion; 46.9 \(\pm 3.0\) ms, after the MesV lesion; \(n = 6\), Table 2).

On the other hand, the temporal relationship between the onset of the FMR and that of the masticatory force reversed after the MesV lesion \((-14.6 \pm 8.3\) ms before the MesV lesion; 37.3 \(\pm 11.5\) ms after the MesV lesion; Table 2). These findings demonstrate that the MesV neurons are responsible for the appearance of the FMR preceding the onset of the masticatory force, and thus for the putative feed-forward phenomenon.

Hardness-dependent change in the FMR after the MesV lesion

The relationship between the magnitude of the FMR and the strip hardness was also compared before (●, Fig. 7) and after the MesV lesion (○, Fig. 7). The ordinate indicates the magnitude of the FMR represented as the percentage of the EMG activity in the control cycle. The mean value of the FMR before the MesV lesion was 341.5% for the hardest strip (no. 5) and 154.0% for the softest strip (no. 1). The FMR increased significantly with increasing strip hardness \((P < 0.005, \text{ANOVA})\). On the other hand, the rate of hardness-dependent increase in the FMR decreased significantly after the MesV lesion \((P < 0.005, \text{ANOVA})\), where the mean value was 248.6% for the hardest strip and 119.0% for the softest strip. It was noted, however, that even after the MesV lesion, the FMR still increased significantly with increasing strip hardness \((P < 0.005, \text{ANOVA})\).

Analysis of the FMR onset in the first five experimental cycles after trigeminal sensory deprivation

The temporal relationship between the onset of the FMR and that of the masticatory force was sequentially analyzed on the first five cycles after combined denervation of the maxillary and inferior alveolar nerves and also after the MesV lesion. The results are shown in Fig. 4A. After the denervation, the onset of the FMR preceded the force onset by 14.0 \(\pm 5.1\) ms in E2 to E5, while the FMR in E1 was elicited at 42.7 \(\pm 18.6\) ms \((n = 5)\) after the force onset. The onset of the FMR in E2 to E5 significantly preceded that of E1 \((P < 0.001, \text{ANOVA}; P < 0.001, \text{Scheffe’s } F\text{-test})\), while there was no significant difference in the FMR onset among the cycles from E2 through E5 (Fig. 4A, ●). After the MesV lesion, however, the temporal relationship between the FMR onset and the force onset was 38.8 \(\pm 10.6\) ms \((n = 6\), average in the 5 cycles) in E2 to E5 as well as in E1. No significant difference was recognized among the five cycles from E1 to E5 (Fig. 4A, ○).

Effect of CMA ablation on the timing of FMR

To examine whether the timing of the FMR was controlled via the transcortical loop, the effect of CMA ablation on the...
FMR onset was evaluated. As shown in Fig. 8A, rhythmical jaw movements were induced by stimulation of the pyramidal tract at the site shown in Fig. 8B. The force appeared 44.0 ms after the maximum jaw opening both before and after the CMA ablation (△, Fig. 8C). The onset of the FMR preceded the force onset by 17.8 ms before CMA ablation and by 24.6 ms after

### Table 1. Summarized results of the temporal relationships between the maximum jaw opening and the force onset, and between the force onset and the FMR onset in the first five experimental cycles

<table>
<thead>
<tr>
<th>Parameter Analyzed</th>
<th>n</th>
<th>E1, ms</th>
<th>E2, ms</th>
<th>E3, ms</th>
<th>E4, ms</th>
<th>E5, ms</th>
<th>Significant Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>20</td>
<td>44.7 ± 1.8</td>
<td>44.6 ± 2.0</td>
<td>44.4 ± 1.8</td>
<td>44.7 ± 2.0</td>
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<td>Maximum jaw opening, force onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Force onset, FMR onset</td>
<td></td>
<td>44.9 ± 15.3</td>
<td>12.9 ± 9.0</td>
<td>14.5 ± 8.5</td>
<td>15.6 ± 8.9</td>
<td>15.2 ± 8.6</td>
<td>s</td>
</tr>
<tr>
<td>Force onset, FMR onset</td>
<td></td>
<td>42.7 ± 18.6</td>
<td>13.5 ± 4.8</td>
<td>14.1 ± 5.2</td>
<td>14.4 ± 5.4</td>
<td>13.9 ± 4.9</td>
<td>s</td>
</tr>
<tr>
<td>Denervation</td>
<td>5</td>
<td>43.7 ± 2.2</td>
<td>44.2 ± 1.4</td>
<td>43.78 ± 2.9</td>
<td>43.4 ± 3.1</td>
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<td>ns</td>
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<tr>
<td>MesV lesion</td>
<td>6</td>
<td>46.9 ± 5.0</td>
<td>46.6 ± 3.2</td>
<td>45.9 ± 3.8</td>
<td>47.4 ± 5.2</td>
<td>46.9 ± 4.6</td>
<td>ns</td>
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<tr>
<td>Force onset, FMR onset</td>
<td></td>
<td>41.4 ± 10.2</td>
<td>37.9 ± 12.7</td>
<td>37.4 ± 11.5</td>
<td>38.7 ± 9.3</td>
<td>38.4 ± 9.3</td>
<td>ns</td>
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</table>

Values are means ± SD. Negative values of the mean indicate that the facilitatory masseteric response (FMR) onset preceded the force onset. Significant difference was tested between the cycle E1 and each of the cycles E2 to E5. n, number of samples; ns, not significant; s, significant at the level of $P < 0.001$.

Note that the onset of FMR did not precede the force onset after the MesV lesion.

FMR onset was evaluated. As shown in Fig. 8A, rhythmical jaw movements were induced by stimulation of the pyramidal tract at the site shown in Fig. 8B. The force appeared 44.0 ms after the maximum jaw opening both before and after the CMA ablation (△, Fig. 8C). The onset of the FMR preceded the force onset by 17.8 ms before CMA ablation and by 24.6 ms after

**Fig. 5.** Effect of trigeminal deafferentation on the relationship between the FMR onset and the force onset. A: an example of recordings of masticatory force, masseteric EMG, and jaw movement after combined denervation of the maxillary and inferior alveolar nerves. The same animal as in Fig. 2. B: relationship between the FMR onset and the force onset before and after denervation. The lines and symbols are the same as those of Fig. 2. Note that no change occurred in the relationship after the denervation.
TABLE 2. Summarized results of the temporal relationships between the maximum jaw opening and the force onset, and between the force onset and the FMR onset

<table>
<thead>
<tr>
<th>Parameter Analyzed</th>
<th>Before the Experiment, n</th>
<th>After the Experiment, ms</th>
<th>Significant Difference, ms</th>
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<tr>
<td>Maximum jaw opening, force onset</td>
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<td>44.2 ± 2.0</td>
<td>43.2 ± 2.2</td>
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<tr>
<td>Force onset, FMR onset</td>
<td></td>
<td>−15.0 ± 12.6</td>
<td>−12.9 ± 9.8</td>
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<tr>
<td>MesV lesion</td>
<td>6</td>
<td>45.1 ± 1.7</td>
<td>46.9 ± 3.0</td>
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<tr>
<td>Maximum jaw opening, force onset</td>
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<td>−14.6 ± 8.3</td>
<td>37.3 ± 11.5</td>
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<tr>
<td>Force onset, FMR onset</td>
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<tr>
<td>CMA ablation</td>
<td>5</td>
<td>43.6 ± 2.0</td>
<td>44.9 ± 4.2</td>
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<tr>
<td>Maximum jaw opening, force onset</td>
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<td>Force onset, FMR onset</td>
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<tr>
<td>Values are means ± SD. The signs are the same as those in Table 1. CMA, cortical masticatory area.</td>
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CMA ablation (▲, Fig. 8C). Table 2 shows the summary of the results obtained from five rabbits with CMA ablation. No significant differences were recognized before and after the CMA ablation in terms of the temporal relationship between the force onset and the maximum jaw opening (43.6 ± 2.0 ms before CMA ablation; 44.9 ± 4.2 ms after CMA ablation; n = 5, Table 2). The temporal relationship between the FMR onset and the force onset was not affected by the CMA ablation (−14.7 ± 2.8 ms before CMA ablation; −14.6 ± 9.4 ms after CMA ablation; Table 2). The FMR onset still preceded the force onset after the CMA ablation.

DISCUSSION

Feed-forward control of the FMR

The present study strongly suggests that jaw-closing muscle activity is modulated in a feed-forward manner during CRJMs in the anesthetized rabbits. When a thin plastic test strip was placed between the opposing molars during CRJMs, the masseteric activity was facilitated, and its onset could precede the onset of the masticatory force, which confirms the results of a previous study (Hidaka et al. 1997). The temporal relationship between the masseteric activity and the masticatory force was further analyzed on the first five masticatory cycles with strip application. It was found that the FMR did not precede the force onset during the first experimental cycle (E1) but did in the subsequent four experimental cycles (E2 to E5) in the control rabbits. Similar findings have been reported in human studies (Abbink et al. 1999; Ottenhoff et al. 1992a,b, 1993; Van Der Bilt et al. 1995). When an external force simulating food resistance was introduced while the subjects were making rhythmical open-close jaw movements, AMA was induced to overcome the resistance. The AMA appeared after the onset of the force in the first cycle after introduction of the force, while it started before the onset of the force in the subsequent cycles. The present study reveals that the putative feed-forward mechanism can function even when the rabbits are under an anesthetized state. This result suggests that there are fundamental neural circuits, probably at the level of the lower brain, which are activated to advance activity of the jaw-closing muscles during chewing. This matter is discussed later.

During voluntary movements, sensory feedback via the reflex arc has an important role in the modulation of muscle activity. However, the delays in most reflex arcs are large, making feedback control too slow to account for rapid movement. Thus the concept of feed-forward control, in which the actions are preprogrammed using previous sensory information, has been proposed as the mechanism for rapid and smooth movements (Blakemore et al. 1998; Wolpert 1997; Wolpert et al. 1995). Such a mechanism has been proposed in the control of the EMG activity in the hindlimb muscles of the cat during locomotion. For example, Engberg and Lundberg (1969) described in intact cats an extensor burst that occurred prior to touchdown of the hind limb, from which they conclude that the onset of the extensor activity is centrally preprogrammed. Feed-forward control has also been proposed in goal-oriented...
volitional movements (Kawato et al. 1987), which allows a goal to be rapidly and smoothly obtained. The present finding suggests that the feed-forward control mechanism is a general mechanism, participating even in regularly repeated movements like mastication. Ottenhoff et al. (1992a,b) proposed that the function of the anticipatory response of the AMA during natural chewing was of importance for dampening the perturbation of the chewing movement at the moment of food contact. We have noted that horizontal movements of the jaw during the power phase were greater in the cycles with an early appearance of the FMR (E2 to E5) than those in the cycles without it (E1). Since the power phase is the main phase to crush and grind the chewed substances, the increment of the horizontal jaw movements due to feed-forward control of jaw-closing muscle activities at this phase makes mastication more powerful and efficient.

Sensory inputs involved in putative feed-forward control

Ottenhoff et al. (1992a,b) proposed that the open-loop (feed-forward) mechanism functions in such a way that the sensory information in the previous cycles is integrated to program the onset of the AMA in the following cycles. However, they did not evaluate the kind of sensory receptors that is responsible for this mechanism. The present study shows that the onset of the FMR did not precede the force onset after MesV lesion, which means that the putative feed-forward phenomenon disappeared after the lesion. This observation does not necessarily indicate that the muscle spindles alone contribute to this phenomenon, because not all of the MesV neurons are ganglion cells of muscle spindle afferents. Some neurons are ganglion cells of the periodontal and other afferents, although the muscle spindle afferents and periodontal ones are two major inputs to the MesV (Jerge 1964; Nomura and Mizuno 1985). However, since the temporal relationship of the onset of the FMR, relative to that of the masticatory force, was not affected significantly by combined denervation of the maxillary and inferior alveolar nerves, the periodontal afferents may not be primarily responsible for the putative feed-forward control of the FMR. The inputs from the muscle spindles may thus be mainly responsible for this type of control of the jaw-closing muscle activity.

The above conclusion is well supported by the findings of
previous studies where recordings were made from muscle spindle discharges from the MesV. The firing rate of muscle spindle units increased during chewing in both the awake and anesthetized animals (Hidaka et al. 1999; Masuda et al. 1997; Taylor 1981). Hidaka et al. (1999) examined the relationship of the muscle spindle discharges to the phases of a masticatory cycle during CRJMs. It is of interest that the discharges generally increased in all three phases (jaw-opening, jaw-closing, and power phases) when the test strip was applied. However, only the discharge rate during the power phase increased in a hardness-dependent manner, not during the other phases. Hidaka et al. (1999) proposed that the putative feed-forward phenomenon of the FMR is related to the increased firing rate of the jaw-opening phase. We recently found that the FMR onset was not affected by the change in strip thickness and hardness, which accords with the proposition that the muscle spindle activity that occurs during jaw closing does not modulate the timing of the FMR onset (Komuro et al. 2001). If we combine the present and previous results (Hidaka et al. 1999; Komuro et al. 2001), discharges of the muscle spindle afferents in the jaw-opening phase of the previous cycle may be responsible for the feed-forward phenomenon that appeared in the subsequent cycles.

**Hardness-dependent change of the FMR after MesV lesion**

The FMR was still modulated in a hardness-dependent manner after the MesV lesion, while the putative feed-forward phenomenon of the FMR disappeared. There are at least two possible reasons to explain the difference in the effects. One is that some collaterals of the peripheral axons of the MesV neurons that establish direct synaptic contact with the trigeminal motoneurons (Shigenaga et al. 1988) were not completely destroyed when the MesV was lesioned because of their anatomical configuration. The reflex pathway via these remaining collaterals may contribute to induce the FMR, but not to induce the putative feed-forward phenomenon. The other explanation is that periodontal receptors may be involved with the control of the magnitude of the FMR more strongly than with the temporal control of the FMR. In a previous study, the hardness-dependent modulation of the FMR tended to decrease after periodontal deafferentation, although the effects were not regarded as significant (Hidaka et al. 1997). Moreover, combined destruction of the periodontal afferents and muscle spindle afferents diminished the FMR almost completely, while destruction of either one of both afferents could not completely diminish the FMR (Inoue et al. 1989; Lavigne et al. 1987; Morimoto et al. 1989). It is probable that the timing of the FMR is mostly controlled by the muscle spindles, while the magnitude of the FMR is controlled mainly by the muscle spindles and partly by the periodontal receptors.

**Central neural pathway for putative feed-forward control**

The central neuronal circuits involved in the feed-forward mechanism have not been analyzed in detail, especially the involvement of the cerebral cortex. The projection of low-threshold muscle afferents from the masticatory muscle to the cerebral cortex has been reported in the cat and the monkey (Lund and Sessle 1974; Sirisko and Sessle 1983). In addition, a possible transcortical response has been suggested for masticatory muscles (Marsden et al. 1976). Although decisive evidence is still lacking to show that muscle spindle afferent inputs can drive the pyramidal tract neurons of the jaw motor area or the CMA, as has been shown for limb muscle afferents (Conrad et al. 1974; Tanji and Wise 1981), there is a possibility that the putative feed-forward phenomenon is induced via the transcortical loop. However, the present study showed that after CMA ablation, the onset of the FMR still preceded the force onset during the rhythmic jaw movements evoked by stimulation of the pyramidal tract. Therefore the CMA may not be responsible for the putative feed-forward control of the FMR. However, it is still possible that the cortical sensory projection area of the oral-facial region remained after the CMA ablation, which may induce the precedence of the FMR onset. Examining the relationship between the oral sensory projection areas and the CMA, Masuda (1991) reported that the cortical projection areas of the contralateral alveolar inferior and lingual nerves overlapped well on the CMA. This finding accords with the Woolsey’s view that the rabbit’s motor cortex is a sensory-motor cortex (Woolsey 1958). The cortical area ablated in the present study was greater than the CMA, including the projection areas of both the alveolar inferior nerve and the lingual nerve. Therefore contribution of the transcortical loop to the putative feed-forward phenomenon of the FMR may be minor, if any. It should be mentioned, however, that the present results do not deny the involvement of the cerebral cortex in the feed-forward control of the jaw movements in conscious animals. It is also possible that ipsilateral orofacial afferent projections to the CMA of the other side (Huang et al. 1989; Lund et al. 1974) may still have been operational after unilateral CMA ablation. Nonetheless, the findings obtained in the present study were similar to those observed in our preliminary study using rabbits with bilateral CMA ablation.

The cerebellum is another candidate for the neuronal circuits involved in the putative feed-forward control of the FMR, because it is reported that the cerebellum is certainly concerned with the feed-forward control of hand and arm movements (Dugas and Smith 1992; Espinoza and Smith 1990). We recently reported that the precedence of the FMR onset due to strip application during CRJMs was nearly abolished by cerebellar ablation (Komuro et al. 1999). Thus the cerebellum may be involved in the putative feed-forward control of masseteric EMG activity. Anatomical studies have demonstrated direct and indirect projections from the masseteric muscle spindle afferents to the cerebellum (Darian-Smith and Phillips 1964; Dessem et al. 1997; Donga and Dessem 1993; Elias 1990). In addition, the cerebellar nuclei outputs affect rhythmical jaw movements (Katayama et al. 1992, 1993; Nakamura and Kataoka 1995). It is assumed that the cerebellum accepts direct and/or indirect inputs from the muscle spindle afferents during the jaw-opening phase of a masticatory cycle, and then the outputs from the cerebellar nuclei function to induce the feed-forward response in the subsequent cycles. Further studies are needed to elucidate the neuronal circuits contributing to the feed-forward control of masticatory jaw movements in detail.
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