Further Studies on the Stereotaxic Thalamotomy for Pain Relief

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YOSHI, N., ADACHI, K., KUDO, T., SHIMIZU, S., NISHIOKA, S. and NAKAHAMA, H. Further Studies on the Stereotaxic Thalamotomy for Pain Relief. Tohoku J. exp. Med., 1970, 102 (3), 225-232 — In animal experiments, the activity of 161 thalamic pulvinar neurons was studied in cats using the following stimuli; bending hairs, tapping the superficial and deep tissues, pinching the skin, scratching the peritoneum, stretching the mesentery, administration of acetylcholine and bradykinin into the mesenteric artery, and presentation of tones and light. Approximately a half of the pulvinar neurons responded to either of these stimuli. Occlusion among somatic, visceral, visual and auditory inputs was a common observation. The stereotaxic thalamotomy was performed on 20 patients suffering from intractable pain. Complete relief of the pain without appreciable sensory loss was obtained in 12 cases, which consisted of 10 cases of malignant tumor and 2 cases of postcerebrovascular disease. Good or fair effect was obtained in 8 cases. The anatomical verification of 2 brains indicated that each of the dorsal pulvinar nucleus, the fornix and the corpus callosum was partially destroyed. It is suggested that excellent effects may be expected, if the operation is performed stereotaxically on patients who need narcotics or strong analgesics for pain relief.

METHODS AND RESULTS

1) Animal experiments

The experiments dealt with the single units of the thalamic pulvinar nucleus in cats. The methods and techniques used in this study were essentially the same as those

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described in the previous paper. In the previous experiments, the impulse activity from a single unit was recorded through tungsten electrodes, but in the present experiments stainless steel microelectrodes were used. At the end of the experiment, currents of 10 μA were passed through each electrode for 20 seconds to mark the position of the electrode tip. After cats were sacrificed by intravenous injection of pentobarbitone sodium, 10% formalin solution containing about 2% potassium ferrocyanide was perfused through the carotid artery. Frontal serial frozen sections of 25 μ in thickness were stained with 0.2% cresyl violet, and the approximate recording sites were determined. Abdominal stimuli were offered in such ways as scratching the peritoneum and stretching the mesentery through a midline abdominal small incision. When it is necessary, 1–5 μg of synthetic bradykinin (Sandoz) and 100–200 μg of acetylcholine were administered into the mesenteric artery through a polyvinyl cannula.

The activities of 161 units have been recorded after the publication of our previous paper. Out of these units, 72 were examined with various stimuli such as bending hairs with an air-puff, pinching the skin with toothed forceps, scratching the peritoneum, stretching the mesentery, and the presentation of tones and light. Scratching the peritoneum and stretching the mesentery were designated as abdominal stimuli, since these stimuli were thought to induce the abdominal pain. Therefore, the 72 units were tested with five kinds of stimuli. Out of the 72 units, 36 responded to some kinds of 5 stimuli: 16 responded to one kind of stimuli; 10 to 2 kinds; 8 to 3 kinds; 2 to 4 kinds; and 0 to 5 kinds of stimuli. Twenty units (27.8%) received polysensory inputs from the skin, abdomen, cochlea, and retina. Some examples of receptive fields of the pulvinar units responsive to somatic stimuli are shown in Fig. 1. In addition, the units activated by abdominal and light stimuli are indicated near each drawing in this figure. Out of 72 units examined, 2 responded to abdominal and pinch stimuli as seen in units Pul. 1029; 3 to abdominal stimuli and hair bending, as in unit Pul. 1040; 6 to abdominal and light stimuli and hair bending, as in unit Pul. 1023; 1 to abdominal and pinch stimuli and hair bending, as in unit Pul. 1028; and 2 to abdominal, pinch and light stimuli and hair bending, as in unit Pul. 1021.

Table 1 shows the summary of 161 pulvinar units studied. The units are classified according to the following peripheral stimuli which excite them: hair bending, tapping
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2) Clinical observations

After the publication of the previous paper, three cases were stereotaxically operated on for pain relief (Table 2). One of these cases had been suffering from intractable, chronic pain induced by postcerebrovascular accident and two from that induced by infiltration and metastasis of malignant tumors. Target point of the stereotaxic operation was located in the pulvinar nucleus. The methods and techniques were similar to those described in the previous paper.

Case 18.—This patient was a 56-year-old woman with numbness, rigidity and pain on the right side of the body. On March 28, 1960, she suddenly became unconscious. She was diagnosed as cerebrovascular disease. She was admitted to our hospital and received the treatment of right-sided hemiparesis. In 1963 she had reattack of cerebrovascular accident followed by right hemiplegia, and was diagnosed as the right-sided intracerebral hemorrhage. Hemiplegia gradually decreased, but numbness and pain appeared on the right side of the body. Pain was almost continuous and was relieved with analgesics such as Pyrabital.

On April 16, 1968, bilateral stereotaxic operation was performed. Good effect was transiently obtained for pain relief. However, pain reappeared occasionally on the right side of the body since 2 days after the operation. Numbness did not vanish postoperatively. No emotional disturbance was noted.

Case 19.—This patient was a 46-year-old woman suffering from abdominal pain. In the beginning of September of 1968, she had felt hypochondriac and epigastric pain. Pain became very severe in October, and spread to the right hypochondriac region and lumbar area. She was diagnosed as stomach cancer with metastasis to other organs, especially to the retroperitoneum, on October 14, 1968. Opystan (meperidine) and Noblon (Pyrabital + chlorpromazine + chlorpheniramine) was given frequently (5–8 times a day) every day.

On October 29, 1968, bilateral stereotaxic operation was performed. No response was produced by the electrical stimulation to the target point before the destruction. After the destruction spontaneous pain vanished completely. No emotional or psychic disturbance was observed. The patient died of a sudden intestinal bleeding 10 days after the operation.

Case 20.—This patient was a 52-year-old man suffering from pain of the right foreneck. Partial gastric and esophageal resections were performed on November 1, 1967, and diagnosed as gastric sarcoma with the metastasis of esophagus. In March, 1968, a tumor was found at the right foreneck. However, the neck tumor became larger and pain

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**TABLE 1. Results obtained from 161 pulvinar neurons**

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Number of units examined</th>
<th>Number of units responsive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair bending</td>
<td>152</td>
<td>42 (27.6%)</td>
</tr>
<tr>
<td>Tapping</td>
<td>84</td>
<td>7 ( 8.3%)</td>
</tr>
<tr>
<td>Pinch</td>
<td>141</td>
<td>14 ( 9.9%)</td>
</tr>
<tr>
<td>Abdominal stimuli</td>
<td>99</td>
<td>32 (32.3%)</td>
</tr>
<tr>
<td>Tone</td>
<td>114</td>
<td>7 ( 6.1%)</td>
</tr>
<tr>
<td>Light</td>
<td>139</td>
<td>29 (20.9%)</td>
</tr>
</tbody>
</table>

the superficial and deep tissues, pinching the skin, abdominal stimuli, and tone and light stimuli. Out of 99 units examined with abdominal stimuli, 32 (32.3%) were responsive; out of 152 units with hair bending, 42 (27.6%) were responsive; and out of 139 units with light stimulus, 29 (20.9%) were responsive. A few units responded to other stimuli.
ocurred at the right foreneck on August 2, 1968, and intermittent Cobalt 60 radiation was applied from August through November, 1968. In the beginning of September the pain became very severe.

December 10, 1968, bilateral stereotaxic operation was performed. After the operation the spontaneous pain disappeared completely until his death on January 30, 1969. No emotional disturbance was noted.

A total of 20 cases, including 17 cases reported previously,1 received stereotaxic operation for pain relief. Complete relief of chronic, intractable pain without appreciable sensory loss was obtained in 12 cases, which consisted of 10 cases of malignant tumor and 2 cases of post-cerebrovascular disease. Good or fair relief of pain was obtained in the remaining eight cases.

In the assessment of the degree of pain before the surgical procedure, it seems important to try medication for relieving pain. Narcotics with strong analgesic action were used in some patients before the admission to our hospital. However, it was difficult to determine whether such medication was appropriate for pain relief. Therefore on admission all medications were taken out, and placebo or mild analgesics such as Pyrabital were given at first. Some patients who had received narcotics were relieved from pain by the administration of placebo or mild analgesics. Out of 20 cases, 11 required narcotics, but 9 did not. All the patients requiring narcotics who consist of 9 cases of malignant tumor and 2 cases of cerebrovascular disease obtained complete relief of pain after the surgical operation, while 8 patients who did not need narcotics for pain relief did not show complete relief of pain postoperatively. From these results it seems necessary to make the operation in the patients who need narcotics or strong analgesics, after appropriate kind and adequate dosage of medicaments have been determined.

Beside the medication, subjective complaints of pain including its nature and severity seemed to be important as indices of the degree of pain. Five cases felt 'burning pain'; 3 cases, pain 'like being torn into pieces'; and 10 cases, pain 'like pin and needle pricking'. Colic pain was noted in 2 cases. Complete relief of pain was obtained in all cases suffering from 'burning pain', 'being torn into pieces' and colic pain. Among 10 cases suffering from pain 'like pin and needle pricking pain', only three were completely relieved from intractable pain.

3) The verification of the sites of lesion produced by stereotaxic operation

The brains from 2 patients who suffered from cancer and were completely relieved from intractable, and chronic pain after the site of stereotaxic operation was examined histologically (Cases 6 and 12 described in our previous paper1). The brains were removed, and fixed in 10% formalin. The involved thalamus with surrounding structures was cut out.
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### Stereotaxic Operation

<table>
<thead>
<tr>
<th>Medication</th>
<th>Side of operation</th>
<th>Duration after operation</th>
<th>Effect After operation</th>
<th>Effect Present</th>
<th>Emotional change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyribital Noblon</td>
<td>Bilateral</td>
<td>2 years</td>
<td>#</td>
<td>+</td>
<td>None</td>
</tr>
<tr>
<td>Opystan Noblon</td>
<td>Bilateral</td>
<td>10 days*</td>
<td>#</td>
<td>#</td>
<td>None</td>
</tr>
<tr>
<td>Opystan</td>
<td>Bilateral</td>
<td>7 weeks*</td>
<td>#</td>
<td>#</td>
<td>None</td>
</tr>
</tbody>
</table>

* died, CVA cerebrovascular accident

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*Fig. 2. Bilateral cross sections of the brain from Case 6 showing lesions in the pulvinar nucleus and its surrounding structures. A, sections of the right brain; B, those of the left brain. Cc, corpus callosum; Cd, caudate nucleus; Fx, fornix; G1, lateral geniculate nucleus; Gm, medial geniculate nucleus; Li, nucl. limitans; and Pul, pulvinar nucleus.*

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In a block, embedded in celloidin, and cut at 25 μ, using the frontal serial section technique. Three successive sections at 10-section intervals were stained with Delafield’s hematoxylin for myelin and by both cresyl violet and hematoxylin-eosin for cellular detail. The limits of the lesions were determined by microscopic examination and reconstructed graphically.

A 48-year-old woman (Case 6) had intractable pain in her lumbus and lower abdomen.
with cancer of the uterus. She came to feel no spontaneous pain until her decease, 1 year and 2 months after the stereotaxic operation. Emotional incontinences such as weeping and excitement were noted for 7 days after the operation. Anatomically, the sections of the right brain indicated that the lesion in the dorsomedial part of the pulvinar nucleus measured approximately 4 mm × 5 mm at the largest diameter and extended rostro-caudally throughout the pulvinar nucleus reaching probably the intralaminal nucleus rostrally, and approximately a half of the fornix and of the ventral portion of the corpus callosum were also destroyed extending for 9 mm rostro-caudally (Fig. 2A). Sections of the left brain showed that irregularly shaped lesion in the lateral part of the dorsal pulvinar nucleus measured approximately 5 mm vertically, 4 mm horizontally, and 4 mm rostro-caudally, and a half of the ventral part of the corpus callosum was also destroyed extending for 5 mm rostro-caudally (Fig. 2B).

A 25-year-old man (Case 12) with cancer of the epipharynx suffered from intractable pain in his neck, lower abdomen and left leg. He came to feel no spontaneous pain until his decease, 24 days after the stereotaxic operation. Emotional excitement was noticed for 1 week after the operation. Sections of the right brain showed that the lesion measured 3 mm vertically, 5 mm horizontally, and 3 mm rostro-caudally in the dorsal pulvinar nucleus, and approximately 80% of the fornix were destroyed extending for 3 mm rostro-caudally (Fig. 3A). Sections of the left brain indicated that the lesion measured 3 mm vertically, 2 mm horizontally and 3 mm rostro-caudally in the the dorsal pulvinar nucleus, and almost all of the fornix and approximately a half of the ventral part of the corpus callosum were also destroyed extending for 6 mm rostro-caudally (Fig. 3B).

Fig. 3. Bilateral cross sections of the brain from Case 12 showing lesion sites in the pulvinar nucleus and the surrounding structures. A, a section of the right brain; and B, sections of the left brain.
DISCUSSION

The present study shows that the pulvinar units activated by scratching the peritoneum and/or by stretching the mesentery also responded to the administration of acetylcholine and bradykinin into the mesenteric artery. It is well known that scratching the peritoneum and stretching the mesentery evoke visceral pain in the human. Taira et al. showed that acetylcholine and bradykinin administered into the mesenteric artery induced the nociceptive response of intestine, e.g., vocalization in immature dogs. Lim and Guzman indicated that intraperitoneal injection of bradykinin induced pain sensation in the human. Burch and DePasquale administered bradykinin into the brachial artery of the human, showing that pain sensation began at 30 seconds after administration, became severest after 45 seconds, disappearing after 60–120 seconds, while residual sensation of warmth occurred at 120–180 seconds after administration. In the present study, when bradykinin was administered into the mesenteric artery of the cat, the impulse frequency in the pulvinar neurons increased with a similar time course to that of pain sensation, as described above. From these facts it may be considered that abdominal stimuli employed in this paper evoke abdominal pain in cats. It was found that 32.3% of the pulvinar neurons received nociceptive inputs from the abdomen. This corresponds well with the present clinical observation that the stereotaxic thalamotomy relieved the patients from intractable visceral pain.

Out of 12 patients who had been relieved completely from intractable pain after the stereotaxic operation, 8 died within 4 months after the operation, mainly of the malignant tumor. Therefore it is difficult to determine precisely how long the effect of this operation endures. Other 4 patients who were alive for more than one year after the operation were relieved completely from intractable pain, and such pain did not reappear. Therefore it seems to be probable that such effect may continue more than one year, if we operate the patients who needs narcotics or strong analgesics for pain relief.

The histological results obtained indicate that our stereotaxic operation partially destroyed the dorsal pulvinar nucleus, the fornix and the corpus callosum. However, which site of these regions is essential for pain relief is not clear from the results obtained. This remains to be clarified in future. Heath et al. applied the stimulation to the septal region of human patients, indicating that endogenous pain was relieved for several hours to 2 or 3 days, although exogenous pain by pinprick, and electrical and thermal stimuli was perceived. It is known that fornix fibers form an afferent pathway to the septum. Therefore, it may be probable that fornix lesions were effective in pain relief. Emotional changes induced by the present stereotaxic operations might be due to the destruction of the fornix, since the fornix provides an anatomical substrate for neuronal activity concerned with emotion.

Visceral and somatic pathways were convergent in the pulvinar neurons of cats. This convergence might originate from neurons in Rexed’s laminae V and
VI in the dorsal horn of the spinal cord, since in these regions the convergence between visceral and somatic inputs was found by Selzer and Spencer. 7, 8

Ojemann et al. 9 have shown that anomia was induced by the stimulation of the anterior superior pulvinar in the human patients. Van Buren and Borke 10 noted that the anterior superior pulvinar was destroyed in the brains from patients suffering from speech loss. However, speech disorders were not found in the present study.

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References