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A HISTOLOGICAL STUDY OF SENSORY NERVES IN
THE SMALL INTESTINES AND THE CECUM

by

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I INTRODUCTION

Many investigators have reported various kinds of experiments on visceral sensa-
tion, and they have insisted on the existence of visceral sensation.

Chūji Kimura (Assist. Prof. of our clinic) has proved the existence of sensation
throughout the alimentary canal with his Acetylcholine Method. According to the
results of his physiological experiments, it can be deduced that almost every part of
the viscera is provided with sensory nerves. Visceral sensory nerves are derived
from the bulb, the thoracolumbar and the sacral divisions of the spinal cord. He
determined in his study which part of nerves in these divisions has dominant inner-
vation in each organ.

From the histological standpoint, H. Seto (Prof. of Tohoku University) has re-
ported extensive studies on sensory nerve ending (Seto) in the esophagus, the stom-
mach, the duodenum and the anus. A. Otsu of our clinic has also observed many
sensory nerve endings (Seto) in the jejunum and the sigmoid, where no sensory
nerve ending (Seto) had been demonstrated by Prof. H. Seto. A. Otsu and N.
Tanaka have proved that these sensory nerve endings (Seto) are definitely sensory
nerves. Kimura's physiological findings suggest that sensory nerve endings must
also exist in the ileum, cecum and transverse colon, and that sensory nerves in
these portions arise mostly from the thoracolumbar division of the spinal cord and
partly from the vagus. But this assumption has not yet been proved histologically.

Therefore, I directed my efforts first in finding sensory nerve endings (Seto) in
the small intestines and cecum of human beings, and then systematic observations of
sensory nerve endings (Seto) were done to examine their sensory nature.

II MATERIALS AND METHODS

Only fresh human specimens, taken operatively and fixed immediately after
resection, were stained. I studied mainly normal intestines.

After fixation for 2–3 weeks in 10% neutral formol solution, the specimens
were sliced in thickness of 35μ–45μ parallel to the surface of the mucous membrane
with the freezing microtome. Preparations were stained after fixation in 10% neu-
tral formol solution for more than 4 months.
For systematic observations, laminectomy was performed on dogs under general anesthesia with sodium isomytal. The spinal cord was exposed, the dorsal roots were separated carefully from the ventral roots avoiding injury to the ventral roots, and only the dorsal roots were cut at points distal to their ganglia on both sides. Bilateral vagotomy was performed in the thorax under the positive pressure breathing, cutting both ventral and dorsal branches of the vagus nerves.

The axis-cylinder was stained with Seto's modification of Bielschowsky's silver impregnating method. The myelin sheath was stained with Ehrlich's acid hematoxyline method.

Bielschowsky-Seto's Method
The specimens, which have been cut with the freezing method and kept in neutral formol solution, are
1. washed with distilled water for a few minutes,
2. put into 20% silver nitrate solution, being protected from light, for 24—48 hours,
3. washed in distilled water for 20—30 seconds,
4. put into 20% neutral formol solution.
This solution must be made by diluting the mother neutral formol with only the running water, and placed in 4 or 5 plates. The specimens are transferred to these plates one by one until the white precipitation disappears.
5. washed with running water for 30—50 seconds,
6. placed on filter paper to blot up the water,
7. put into warm ammoniacal silver solution for about 10 minutes,
8. washed with distilled water twice,
9. placed in 0.05—0.1% gold chloride solution for 3—4 hours,
10. placed in 20% sodium thiosulfate solution until the specimens are colored reddish brown,
11. washed in distilled water,
12. dehydrated and mounted.

II SENSORY NERVE ENDINGS IN THE SMALL INTESTINE AND IN THE CECUM

P. Stoehr Jr. and Reiser (1932) presented the theory that the autonomic nerves never terminate freely, but form a fine closed and reticulated structure (Terminalreticulum). This theory has been supported by many authors.

On the basis of Stoehr's theory, H. Seto has studied visceral sensory nerve ending. According to him, the nerves with free terminations can be concluded to be sensory nerves, for autonomic nerve fibers form a closed "Terminalreticulum". He maintains also that these sensory nerve fibers are easily differentiated from the autonomic nerve fibers by their thickness.

A. Otsu and N. Tanaka of our clinic found sensory nerve ending (Seto) in the stomach, the jejunum, the sigmoid and the esophagus, and they proved that sensory nerve endings (Seto) exist in or near the mucous membrane and that they do not
RELAY NEURONS ON THE WAY. They agree with H. Sato's finding, mentioned above, that sensory nerve endings (Sato) can be certainly considered sensory nerves.

In the muscular, submucous and mucous layers of the small intestine and cecum, the "Terminalreticulum" and the "Geschlaengerte Territorien" (winding territories), described by P. Stoehr jr., are found in abundance. Many nerve cells are, of course, found in the myenteric or submucous plexus of these intestines. (Fig. 1, and 2.)

A few myelinated nerve fibers are found in all layers except the mucous membrane in the small intestine and cecum. In some preparations, myelinated nerve fibers were traced through the wall of the intestine to the submucous layer. In the subserous and muscular layers, thick nerve bundles, consisting of a few myelinated and many non-myelinated nerve fibers, are found. But in the submucous layer, myelinated nerve fibers accompanied with few non-myelinated nerve fibers can be found in the mucous membrane.

Myelinated nerve fibers sometimes run through the myenteric or submucous plexus, but no connection can be proved between most of these nerve fibers and the nerve cells in the nerve plexi.

Preganglionic autonomic nerves may be myelinated as well as sensory nerves, but the former can be distinguished from the latter in the periphery, where interposing nerve cells are no longer found and autonomic nerves are changed into reticular structures in their appearance.

1) Sensory nerve endings in the duodenum

In the muscular layer, thick and wavy nerve fibers with varicosities are found among the thin autonomic nerve fibers, and they can be traced through the submucous layer to the muscularis mucosae. After entering the lamina propria mucosae, they sometimes arborize into two branches getting finer, but they never form a "Terminalreticulum". (Fig. 5.) Sometimes, beneath the glands in the lamina propria mucosae, long and winding nerves, distinct from winding territories, can be traced. (Fig. 3, and 4.) We consider them to be sensory nerves.

In the duodenum of dogs, sensory nerve endings arborize in the submucous layer and enter the lamina propria mucosae. (Fig. 6.)

2) Sensory nerve endings in the jejunum

A. Orsu has already reported the existence of sensory nerve endings in the jejunum. In the jejunum of the adult human being, sensory nerve endings (Sato) are found as distinct from autonomic nerve fibers. They are traced from the submucous layer, through the muscularis mucosae and lamina propria mucosae, to simple free endings beside the intestinal glands. These endings probably correspond to the so-called unforked termination (Sato). (Fig. 7, and 8.)

3) Sensory nerve endings in the ileum

All specimens were taken from the distal portion of the ileum.

In the ileum, myelinated nerve fibers are fewer than in other parts of the small intestine, and thick nerve fibers are rather seldom found.

Relatively thick nerve fibers with no connection to nerve cells are traced from
the submucous layer, running through the submucous nerve plexus, to the muscularis mucosae, and they show terminal arborization in the lamina propria mucosae. These arborized nerve fibers are traced among or beneath the glands without entering the gland itself, and they terminate freely as tapering endings, but sometimes their ends, covered with glandular cells, are not recognizable. These nerve fibers are considered sensory nerve endings (SETO), and they belong to the category of simple-arborizing endings (SETO). (Fig. 9, and 10.)

Unforked sensory nerve endings (SETO) are also found in the ileum, and they are traced along the capillaries to the lamina propria mucosae to terminate freely between the intestinal glands. (Fig. 11, and 12.)

Some sensory nerves are thick even in the submucous layer, are accompanied by autonomic nerve fibers, and arborize into two branches to enter the mucous membrane. These endings are also in the category of simple-arborizing endings (SETO). (Fig. 13.)

4) Sensory nerve endings in the cecum

Myelinated nerve fibers in the cecum are more numerous than in the ileum, but the number of thick nerve fibers is about the same as in the ileum.

Sensory nerve endings in the cecum are unforked. They are traced from the submucous layer, running through the muscularis mucosae, in the lamina propria mucosae to terminate freely between the intestinal glands. (Fig. 14, and 15.)

5) Abnormal sensory nerve endings in the duodenal diverticulum

Specimens were taken from the duodenal diverticulum of a patient, who had been suffering from severe abdominal pain. In the wall of this diverticulum, abnormally thick nerve fibers were found winding in the submucous and mucous tissues. These findings are attributed to the pathological changes of the sensory nerves, caused by the chronic inflammation of the diverticulum. (Fig. 16.) But in this case, the "Terminalreticulum" had an almost normal appearance.

The sensory nerve endings in the small intestine and cecum are always of uncomplicated structure (simple-arborizing endings and unforked endings). Neither tangled nor specific organized terminal structures are found.

The sensory nerve endings described above are always nerve fibers themselves, and are quite different from the "Geschlaengerte Territorien" (winding territories), described by P. Stoehr jr. (1954).

Ⅳ SYSTEMATIC OBSERVATIONS OF THE SENSORY INNERVATION OF THE SMALL INTESTINE AND THE CECUM

1) Bilateral posterior rhizotomy

J. N. Langley, O. Forrster, S. W. Ranson, and P. R. Billingsley have maintained, from the histological point of view, that visceral afferent nerves run in the sympathetic trunks, and that most of them are myelinated nerve fibers.

D. Sheehan has proved that the cell bodies of the nerves which reach the VATER-Pacinian corpuscles in the mesenteries are stationed in the spinal ganglia of the dorsal roots of the spinal cord.
I examined the degenerated nerve fibers in the intestine following experimental posterior rhizotomy.

The specimens were taken from dogs with posterior rhizotomy, which had been performed distal to the ganglia of the dorsal roots. The degeneration of the myelinated nerve fibers was examined in the duodenum, jejunum, ileum and cecum of these specimens.

The rhizotomy was performed on the segments from Th. 5 to L. 4, and the experiments were divided in 3 groups as follows.

Group 1...Rhizotomy on Th. 5...Th. 8
Group 2...Rhizotomy on Th. 8...Th. 12
Group 3...Rhizotomy on Th. 13...L. 4

After experimental posterior rhizotomy, myelinated nerve fibers in the small intestine and in the cecum were broken at places giving a beadlike appearance, or stained unhomogeneously, and sometimes degenerating granules were observed in them. All the degenerated nerves, demonstrated in this study, were easily distinguishable from normal myelinated nerve fibers. The nerves whose degeneration was indefinite, were not marked as degenerated nerves.

Group 1. Degenerated nerve fibers are found all over the small intestine, abundantly in the duodenum, sometimes in the distal portion of the small intestine. (Fig. 17.)

Group 2. Degenerated nerve fibers are found in every part of the small intestine, especially in the jejunum most of the myelinated nerve fibers show degeneration. Degenerated nerve fibers are observed also in the cecum. (Fig. 18, 19, and 20.)

Group 3. Degenerated nerve fibers are found in the jejunum, ileum and cecum, but many apparently normal nerve fibers are observed among them. (Fig. 21.)

According to the results of these experiments, the afferent nerves of the small intestine and cecum of dogs are derived from thoracolumbar segments extending from Th. 5 to L. 4, and most of these nerves run via the greater and smaller splanchnic nerves.

The specimens which showed degeneration of the myelin sheath also always showed degeneration of the axis-cylinder with BIELSHOWSKY-SETO's stain. (Fig. 22.) The degeneration of the "Terminalreticulum" is not found after posterior rhizotomy.

2) Vagotomy

In addition to many physiological proofs S. W. RANSON, J. O. FOLEY, and C. D. ALPERT insist on the existence of the afferent nerves in the vagus nerve from the histological point of view also.

Degeneration of the myelinated nerve fibers in the small intestine and cecum was examined after the unilateral (in the neck) and bilateral (in the thorax) vagotomies.

a) Right Vagotomy

Observing 4 ~ 8 days after operation, no degeneration of the myelinated nerve fibers is found.
b) Left Vagotomy

Degenerated nerve fibers were examined 4~14 days after operation. The degeneration of both the myelin sheath and the axis-cylinder is observed in the myenteric plexus of the duodenum 6 days after operation. (Fig. 23, and 24.) But in another specimen, no degeneration is proved in the myelinated and non-myelinated nerve fibers.

c) Bilateral Vagotomy

After unilateral vagotomies, no degenerated nerves were found in the jejunum, ileum and cecum, and even in the duodenum degenerated nerves were not traced further beyond the myenteric plexus. Then both the ventral and the dorsal branches of the vagus nerves were cut in the thorax, and degenerated nerve fibers were sought 6~7 days after operation. But the degenerated nerve fibers were found only in the myenteric plexus of the duodenum. In the small intestines, however, the changes were too uncertain to be called degeneration.

No change was found in the "Terminalreticulum" in these cases.

3) Phrenicotomy

The phrenic nerve forms a nerve plexus beneath the diaphragm, but it is not certain whether it reaches the intestines. No degenerated nerve fibers can be found in the small intestines and cecum after right and left phrenicotomy.

V DISCUSSION

In regard to the peripheral structures of the sensory nerve endings, M. CLARA believes that they have, in common, morphological characteristics which serve to extend their terminal surface. G. WEDDELL maintains that the sensory nerve ending is, in general, a free-ending arborization, and he does not emphasize the complicated structure of the sensory nerve ending. In his view, the same terminal can, under certain conditions, give rise to different sensations.

On the basis of Ström's theory, Prof. H. SETO has found in many organs free-ending nerves which were quite different from the "Terminalreticulum". He maintains that these nerves are sensory nerve endings (SETO), because their peripheral structures are morphologically quite similar to those of the somatic sensory nerves.

According to J. C. WHITE, R. H. SMITHWICK and F. A. SIMBONE, "Viscero-sensory and cutaneous sensory fibers are identical both in histological characteristics and in electrical conduction."

According to the results of my experiments, and also from the morphological point of view, the free ending nerves that I found in the duodenum, jejunum, ileum and cecum, should certainly be considered visceral sensory nerve endings.

Supposing these free ending nerves to be autonomic terminals which innervate the intestinal glands, the nerves are very few in comparison to the number of those glands.

The sensory nerve endings which I found are free ending arborizations or unforked terminations, and they generally have a more simple peripheral structure than those found by H. SETO in the duodenum, stomach and esophagus.
Myelinated nerve fibers are frequently found in the proximal portion of the small intestine, whereas there are few in the ileum. In the small intestines there is only a very small number of myelinated nerve fibers in the submucous layer. In the cecum, the myelinated nerve fibers are more numerous than in the ileum. These findings suggest that the sensory nerves in the large intestine are more abundant than in the small intestine.

I could find no myelinated nerve fiber entering the mucous membrane, though the sensory nerves have been already proved to lose their myelin sheath in the mucous membrane by H. Sêto (in the urinary tract) and by A. Ōtsu (in the stomach).

P. Stoehr Jr. (1954) stated in his study that our sensory nerve endings might be the same as his “Geschlaengerte Territorien”. But our sensory nerve endings are quite different from the “Geschlaengerte Territorien”. They can be easily distinguished from each other.

For the systematic observation of the sensory supply in the small intestine, we traced the myelinated nerve fibers and their secondary degeneration. According to the results of this study, some sensory nerve endings (Sêto) belong to myelinated nerve fibers, and this finding is in agreement with that of A. Ōtsu.

Degeneration of the myelinated nerve fiber is found in the submucous layer of the small intestine and cecum after experimental posterior rhizotomy. In view of the study of J. N. Langley and D. Snehhan, the results of my experiments prove the existence of afferent nerve fibers in the small intestine and cecum, which are derived from the dorsal roots of the thoracolumbar portion of the spinal cord.

On the basis of Ch. Kimura’s physiological experiments, the sensitivity of the small intestine is mediated more dominantly by the afferent nerve fibers in the splanchnic nerves than those in the vagus nerves. The results of my study are generally in agreement with his deduction, but afferent nerve fibers from the vagus nerve are not recognized except for questionable findings in the duodenum.

According to N. Tanaka and A. Ōtsu, vagal afferent nerve fibers can be observed histologically in the esophagus and stomach, and their innervation is more dominant than the sympathetic sensory innervation.

N. Ishikawa, S. Asai, and B. Cannon have proved, from the physiological standpoint, that visceral afferent nerve fibers are contained in the vagus nerve, and that these nerves reach the small intestine and cecum. In my studies, vagotomy caused nerve degeneration in the small intestines, but it was never traced in-wards beyond the muscular layer. This finding is not definite enough to decide the question. Ch. Kimura infers, from the results of his physiological experiments, the dominant vagal afferent innervation of the duodenum. The results of my study, however, do not support his opinion.

The results of many physiological experiments show that afferent nerve fibers in the small intestine and cecum can be derived from the vagus nerve.

Y. Watanabe experimentally proved that vagus nerves can play a role in conducting the noci-stimulation given to the intestine.
In short, the sympathetic afferent fibers derived from the dorsal roots innervate the small intestine and cecum more dominantly than the vagal afferents.

VI CONCLUSION

Using specimens of the small intestine and cecum of human beings and dogs, sensory nerve endings have been sought, and systematic observations of their sensory innervation have been made.

The results are summarized as follows.

1) Sensory nerve endings are found in the mucous membrane of the ileum and cecum. (Human beings)
2) Sensory nerve endings are found in the submucous layer of the dog’s duodenum.
3) Abnormally thick sensory nerve fibers are found in the wall of a duodenal diverticulum.
4) In the small intestine and cecum, no sensory nerve ending with a complicated structure like a corpuscle or end-plates is observed.
5) Afferent nerve fibers of the small intestine and cecum are derived from the dorsal roots of the spinal cord.
6) Vagal afferent nerve fibers of the small intestine and cecum are not traced inwards beyond the myenteric plexus.
7) Sympathetic sensory nerves innervate the small intestine and cecum more dominantly than vagal afferents.
8) Sensory nerve endings, demonstrated in this study, are quite different from the "Geschlaengerte Territorien" (Stoehr).

I am greatly indebted to the kind advice of Prof. Dr. Hachiro Seto (Tohoku University) and also to the constant help of Assist. Prof. Dr. Chuji Kimura during the course of this study.

Explanation of the Figures

2. Roman figures show the number of the magnifications
3. Letters in the figures indicate, Ca.—Capillaries. G.—Glands. Tr.—"Terminal-reticulum"

REFERENCES

Fig. 1. Winding territories in the submucous layer of the ileum. (Human being) S. × 1000.

Fig. 2. Winding territories in the submucous layer of the cecum. (Human being) S. × 1000.

Fig. 3. A sensory nerve ending in the mucous layer of the duodenum. (Human being) S. × 400.

Fig. 4. Drawing from the same preparation as Fig. 3. S. × 400.

Fig. 5. A sensory nerve in the mucous layer of the duodenum. (Human being) S. × 400.

Fig. 6. A sensory nerve ending in the mucous layer of the duodenum. (Dogs) S. × 400.

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Fig. 7. A sensory nerve ending in the mucous layer of the jejunum, (Human being)
S. × 400.

Fig. 9. A sensory nerve ending in the mucous layer of the ileum, (Human being)
S. × 400.

Fig. 11. A sensory nerve ending in the mucous layer of the ileum, (Human being)
S. × 600.

Fig. 8. Drawing from the same preparation as Fig. 7.
S. × 400.

Fig. 10. Drawing from the same preparation as Fig. 9.
S. × 400.

Fig. 12. Drawing from the same preparation as Fig. 11.
S. × 600.
Fig. 13. Sensory nerves in the mucous layer of the ileum. (Human being) S. × 400.

Fig. 15. A sensory nerve ending in the submucous layer of the cecum. (Human being) S. × 400.

Fig. 17. Degenerated nerve fibers in the submucous layer of the duodenum of a dog with posterior rhizotomy. (Th. 5–Th. 8) E. × 400.

Fig. 14. A sensory nerve ending in the submucous layer of the cecum. (Human being) S. × 400.

Fig. 16. Abnormal sensory nerves in the submucous layer of the duodenal diverticulum. (Human being) S. × 400.

Fig. 18. Degenerated nerve fibers in the submucous layer of the duodenum of a dog with posterior rhizotomy (Th. 8–Th. 12) E. × 400.
Fig. 19. Degenerated nerve fibers in the submucous layer of the jejunum of a dog with posterior rhizotomy (Th. 8–Th. 12). E. × 400.

Fig. 20. Degenerated nerve fibers in the submucous layer of the ileum of a dog with posterior rhizotomy (Th. 8–Th. 12). E. × 400.

Fig. 21. Degenerated nerve fibers in the submucous layer of the ileum of a dog with posterior rhizotomy (Th. 13–L. 4). E. × 400.

Fig. 22. Degenerated nerve fibers in the muscular layer of the jejunum of a dog with posterior rhizotomy (Th. 8–Th. 12). S. × 400.

Fig. 23. Degenerated nerve fibers in the myenteric plexus of the duodenum of a dog with L-vagotomy. E. × 400.

Fig. 24. Degenerated nerve fibers in the myenteric plexus of the duodenum of a dog with L-vagotomy. S. × 400.

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和文抄録

小腸及び盲腸の神経の組織学的研究

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牧野 耕治

人及び犬の新鮮な小腸及び盲腸の標本を用い、知覚神経終末を検出し、形態及び分布を観察し、更に実験的に脊髄後根（Th. 5 - L. 4）に通じ、盲腸及び腸間膜神経を切断し、犬の小腸及び盲腸の腸内粘膜神経の次元変性を追求した。

染色は、BIELECHOWSKY 氏鉄血染色法の顕微鏡変形及び EHRICH の神経好酸性染色法を用い、次の結果を得た。

1）人的十二指腸及空腸のみならず、回腸及び盲腸の粘膜にも単純な形状の知覚神経終末（顕微）を見出した。
2）犬の十二指腸及び空腸下組織に知覚神絨終末（顕微）を見出した。
3）小腸竇室の腔内に肥厚せる異状な知覚神絨を観出した。
4）小腸及び盲腸に於ては、複雑な構造を有する知覚神絨終末及び小体または終末の如き構造は観出さなかった。
5）犬の実験に依り、小腸及び盲腸の求心性神経線維は脊髄後根を通る。
6）小腸及び盲腸の逆走性求心性神経線維は腸内神経叡（アウルバッハ氏神経叡）より粘膜側には観出さなかった。
7）交感神経求心性神経叡細は、小腸及び盲腸に於ては、逆走性求心性神絨より優位であった。
8）上記の知覚神絨線維は Ph. Sromer, jr. の言う "Geschlängerte Territorien" とは全く別個の神経線維である。