Changes of Tissue Blood Flow in Mice Loaded with SART (Repeated Cold) Stress or Restraint and Water Immersion Stress and the Effect of Administered Neurotropin

Taeko HATA, Tomitaro KITA, Atsufumi KAWABATA, Eiji ITOH and Yoshitaka NISHIMURA
Department of Pharmacology, Faculty of Pharmacy, Kinki University, Kowakae 3-chome, Higashi-Osaka 577, Japan
Accepted January 31, 1986

Abstract—In order to explore the peripheral microcirculation and to obtain an outline of autonomic innervation in SART (specific alternation of rhythm in temperature)-stressed (repeated cold-stressed) animals, which are regarded as model animals for clinical vagotonic-type dysautonomia, peripheral tissue blood flow was determined in mice, using the hydrogen clearance method. SART-stressed mice showed a decrease in gastric blood flow, no change in hepatic blood flow and an increase in dermal blood flow. In the mice exposed to the restraint and water immersion stress (RWIS), a type of acute stress, in contrast with SART stress which is a subacute type, remarkable decreases were observed in gastric, hepatic and dermal blood flows. Changes of both gastric and dermal blood flow in SART-stressed mice were dose-dependently prevented and maintained within normal limits by the treatment with Neurotropin, a sedative analgesic which is an extract isolated from vaccinia virus-inoculated and inflamed skin of rabbits. In RWIS-loaded mice, Neurotropin exhibited a great preventive effect on changes of blood flow in the stomach, a slight effect in the liver, and no effect in the cutis. When mice were loaded with SART stress after left-cervical vagotomy, SART stress failed to elicit any decrease in gastric blood flow. In SART-stressed mice treated with 6-hydroxydopamine, gastric and dermal blood flows tended to show a further decrease and increase, respectively, over and above the changes caused by SART stress. From these results, it is suggested that SART-stressed mice may have decreased gastric parasympathetic tone, a decrease in sympathetic tone and also other anomalies such as increased tension of the sympathetic cholinergic vasodilator nerves in the cutis.

There have been numerous reports that SART (specific alternation of rhythm in temperature)-stressed (repeated cold-stressed) animals (1, 2), vagotonic-type model animals (3) for clinical autonomic imbalance, show various physiological changes (3–7). With respect to the circulatory system of SART-stressed animals, several abnormalities (5, 6, 8, 9) such as a continuous lowering of blood pressure (5), sympathicotonic-type ECG (electrocardiogram) (6), increases in blood flow in the abdominal aorta and superior mesenteric artery, and decreased blood flow in the common carotid artery (5), have been previously reported.

In the present study, in order to explore the peripheral microcirculatory situation in SART-stressed animals in more detail, we attempted to determine tissue blood flow in mice using the hydrogen clearance method, which was developed by Aukland et al. (10), and has recently been widely applied to measurements of tissue blood flow in various organs. Our present determination of blood flow was carried out in the stomach, liver
and cutis.

Similarly, in mice subjected to restraint and water immersion stress (RWIS) (11-13), a type of acute stress, in contrast with SART stress which is a subacute stress, peripheral tissue blood flow was also estimated. Such RWIS-loaded mice are sympathicotonic in the duodenum and vagotonic in the heart, while SART-stressed mice show vagotonia in the duodenum and sympathicotonia in the heart.

Moreover, the effect of Neurotropin® (NSP), a sedative analgesic, on tissue blood flow changes in both types of stressed mice was studied. NSP is an extract isolated from the inflamed skin of rabbits inoculated with vaccinia virus, and it has been reported (3, 5-8, 14) to be effective against most of the abnormal symptoms observed in SART-stressed animals.

From the viewpoint of systemic symptoms, SART-stressed animals are thought to fall into an autonomically imbalanced vagotonic-type state, considering the results (1, 3) of the mecholyt test, Aschner's oculocardiac test and GSR (galvanic skin response) test, etc. In individual organs, however, the autonomic tensions are differentially imbalanced in this stressed state; for example, partial vagotonia in the small intestine (15, 16) and some blood vessels (5), and sympathicotonia in the heart (6).

Therefore, our further study was carried out on both surgically vagotomized and sympathetic chemically denervated mice exposed to non- or SART-stress in order to consider the differential autonomic activities in each organ from the aspect of tissue blood flow.

Materials and Methods

Healthy male, ddY strain mice were used throughout these experiments.

SART-stress loading: For loading SART stress, mice weighing about 20 g were alternately exposed to 24°C and 4°C temperature at 1-hr intervals from 9 a.m. to 4 p.m., and then the animals were kept at 4°C from 4 p.m. to 9 a.m. the following morning. These procedures were repeated for 5 consecutive days. Stress loading was terminated on the morning of the 6th day, and then the experiments were carried out.

RWIS loading: RWIS loading was performed according to the method (11) reported previously. Each mouse weighing about 25 g was restrained in a wire cylinder, and immersed in 15°C water vertically up to the level of the xiphoid process. The water immersion was continued for 1 hr, since the autonomic imbalances consisting of sympathicotonia in the duodenum and vagotonia in the heart were considered to be most obvious following 1-hr immersion, on the basis of our previous studies (11). Blood flow measurements were carried out 20 to 30 min after the termination of RWIS loading.

Tissue blood flow determination: In the measuring circuit, the diffusion current generated by H2 was detected and amplified by a blood flow meter (Unique Medical, UH-Meter, PHG-201) based on the hydrogen clearance method. The H2 clearance curves were drawn with a pen recorder (Yokogawa Electric Works, type-3056), and flow values were simultaneously calculated by a digital data unit (Unique Medical, DDU-101) based on the height over area technique (17). The determination of tissue blood flow was carried out under urethane anesthesia, with regard to the following 6 positions: the subserous part of the body and pyloric regions of the stomach, the quadrate and left lobes of the liver, and the subcutaneous tissue of the shoulder and lumbar region. As an indicator electrode, a platinum wire-type electrode (Unique Medical, UHE-201) was used, which was conducted to each of the tissues by an injection needle (27 gauge).

Drug administration: In the case of SART-stressed mice, NSP (Nippon Zoki) was i.p. administered once a day for stressing and 6 times altogether, and blood flow was estimated 2 hr after the last treatment. Likewise, in the case of experiments using RWIS mice, the mice were pretreated 6 times in all with daily NSP and then loaded with stress from 1 hr after the last drug administration.

Vagotomy: The left vagus nerve of mice was cut under sodium pentobarbital (Abbott, Nembutal®) anesthesia. As a sham operation, the left vagus nerve was detached but not cut. Estimates of blood flow were undertaken 10 days after both of the above operations.
Sympathetic chemical denervation: An adrenergic degenerator, 6-hydroxydopamine, was used for producing chemical denervation. The extent of nerve destruction caused by 6-hydroxydopamine, varies with organs and according to its doses and administration schedules (18–21). Each investigator used a different animal and organ. Porter et al. (18) reported that the norepinephrine content in the mouse heart was most decreased 2 days after a single administration of 6-hydroxydopamine at a dose of 5 mg/kg. Goldman and Jacobowitz (19) reported that norepinephrine contents in the heart and submaxillary gland were smallest 2–24 hr after a single administration of 6-hydroxydopamine to rats. Other investigators used larger doses and other methods. In this study, we used 5 mg/kg, a relatively smaller dose and 50 or 100 mg/kg, a relatively larger dose. When the influence on manifestation of stress, not on the state after stressing, was studied, 5 mg/kg was administered every 2 days from just before the start of stressing and for the period of stressing. That is, in our present experiments, 6-hydroxydopamine hydrobromide (6-OH-DA, Aldrich) was i.p. administered according to the following two schedules: 1) 5 mg/kg/2 days×3 and 2) 50 or 100 mg/kg×1. Blood flow measurements were carried out on the day following the last treatment in the former schedule and at 2–3 hr after administration in the latter, respectively. In the case of studying the relation to SART stress, 1) the mice received 5 mg/kg of 6-OH-DA every 2 days, 3 times altogether from the first day of stressing until the day preceding the experiment or 2) the SART-stressed mice received 100 mg/kg once 2–3 hr before the flow estimates, after the termination of stress loading.

Statistical analysis: All data obtained were represented by the mean±S.E., and examined for significant differences by Student's t-test.

Results

1) Changes of tissue blood flow in SART-stressed and RWIS-loaded mice: Figure 1 indicates the tissue blood flow in the stomach, liver and cutis of normal and SART-stressed mice. The gastric blood flow was 3.43±0.06 ml/min/g for the body region and 3.14±0.06 for the pyloric region in normal mice, and 2.78±0.06 and 2.48±0.06 in SART-stressed mice, respectively. Both the flow values obtained from SART-stressed mice were significantly (P<0.001) smaller and about 80% compared with the normal values.

The hepatic blood flow was about 1.3 ml/min/g for both the quadrate and left lobes in normal mice, and similar values were also obtained from SART-stressed mice. No sig-

| Organ | Blood flow (ml/min/g) (Mean±S.E.) | % Ratio (S/N) |
|-------|----------------------------------|---------------|
| Stomach |                               |               |
| Body of stomach | 0  1  2  3  4 |               |
| N     |                     |               |
| S     |                     |               |
| Pyloric part | 0  1  2  3  4 |               |
| N     |                     |               |
| S     |                     |               |
| Liver |                               |               |
| Quadrate lobe | 0  0.5  1.0  1.5 |               |
| N     |                     |               |
| S     |                     |               |
| Left lobe | 0  0.5  1.0  1.5 |               |
| N     |                     |               |
| S     |                     |               |
| Mean blood flow |               |               |
| N     |                     |               |
| S     |                     |               |
| Cutis |                               |               |
| Shoulder | 0  0.2  0.4  0.6  0.8 |               |
| N     |                     |               |
| S     |                     |               |
| Lumbar | 0  0.2  0.4  0.6  0.8 |               |
| N     |                     |               |
| S     |                     |               |

Fig. 1. Tissue blood flow in normal and SART-stressed mice measured by the hydrogen clearance method. □: Normal mice (N) and ■: SART-stressed mice (S). No. of mice: 30, 15 and 25/normal group and 30, 16 and 21/SART group, for the stomach, liver and cutis, respectively. ***P<0.001 (t-test).
significant difference was recognized in hepatic flow values between normal and SART-stressed groups.

With regard to the subcutaneous tissue, flow values of 0.47–0.52 ml/min/g were recorded on the shoulder and lumbar region in normal mice. In SART-stressed mice, the dermal blood flow in either region was significantly (P<0.001) increased to above 128% of normal control values.

Figure 2 shows the gastric, hepatic and dermal blood flows in RWIS-loaded mice, as compared to those in normal mice.

In RWIS-loaded mice, the gastric blood flow in both the body and pyloric regions was uniformly and conspicuously reduced to about 45% of normal flow values, and then these decreases were significant (P<0.001).

It was also seen that hepatic blood flow was significantly (P<0.001) decreased after exposure to RWIS, being 40.5–43.5% of normal values, which was similar to the magnitude of the decrease in gastric blood flow.

Likewise, as regards to the cutis, RWIS-loaded mice revealed a considerable decrease in subcutaneous tissue blood flow, in contrast with the increase seen in SART-stressed mice.

2) Action of NSP on tissue blood flow changes in SART-stressed and RWIS-loaded mice: As described above, SART-stressed mice showed a decrease in gastric blood flow and an increase in dermal blood flow, and RWIS-loaded mice showed remarkable decreases in all tissue blood flows including hepatic blood flow. The action of NSP was then examined on these stress-induced changes in tissue blood flow.

Effects of NSP on the gastric blood flow decrease and the dermal blood flow increase in SART-stressed mice are presented in Fig. 3 and Fig. 4, respectively.

As seen in Fig. 3, consecutive administrations of NSP, 100 and 150 mg/kg/day, to non-stressed mice had no significant influence on gastric blood flow. On the other hand, in SART-stressed mice, the decrease in gastric blood flow was significantly (P<0.01–0.001) and dose-dependently prevented by 100 and 150 mg/kg/day of NSP in both the body and pyloric regions, although no such effect was noted with a dose of 50 mg/kg/day of NSP. Treatment with 150 mg/kg/day of NSP, in particular, resulted in remarkable prevention of the blood flow decrease to a normal level.

As shown in Fig. 4, dermal blood flow in non-stressed mice was also not significantly altered by continued NSP treatment. By contrast, the dermal blood flow decrease in SART-stressed mice was dose-dependently blocked by consecutive administration of NSP to the normal flow level, as seen in the case of the gastric blood flow decrease.

Figure 5 indicates the effect of NSP in RWIS mice.

The marked decrease in gastric blood flow following RWIS loading was significantly
Fig. 3. Effects of NSP on gastric blood flow in non- and SART-stressed mice. No. of mice: 5–10/drug-administered group and 10–16/control group. *P<0.05, **P<0.01 and ***P<0.001, compared to the non-stressed control, and *P<0.05, **P<0.01 and ***P<0.001, compared to the SART-stressed control (t-test).

| Drug & Dose (mg/kg/day x 6) | Blood flow (ml/min/g) (Mean±S.E.) | Body of stomach | Pyloric part |
|-----------------------------|-----------------------------------|-----------------|-------------|
| Non-stressed Control        |                                   |                 |             |
| NSP 100                     |                                   |                 |             |
| s 150                       |                                   |                 |             |
| SART-stressed Control       |                                   |                 |             |
| NSP 50                      |                                   |                 |             |
| s 100                       |                                   |                 |             |
| s 150                       |                                   |                 |             |

Fig. 4. Effects of NSP on dermal blood flow in non- and SART-stressed mice. No. of mice: 5–8/drug-administered group and 8–12/control group. **P<0.01 and ***P<0.001, compared to non-stressed control, and *P<0.05, **P<0.01 and ***P<0.001, compared to SART-stressed control (t-test).

| Drug & Dose (mg/kg/day x 6) | Blood flow (ml/min/g) (Mean±S.E.) | Shoulder | Lumbar |
|-----------------------------|-----------------------------------|----------|--------|
| Non-stressed Control        |                                   |          |        |
| NSP 100                     |                                   |          |        |
| s 150                       |                                   |          |        |
| SART-stressed Control       |                                   |          |        |
| NSP 50                      |                                   |          |        |
| s 100                       |                                   |          |        |
| s 150                       |                                   |          |        |

Fig. 5. Effects of NSP on tissue blood flow in RWIS mice. □: Non-stress (N) and □: RWIS (R). No. of mice: 6–16/group. *P<0.05, **P<0.01 and ***P<0.001, compared to non-stressed control, and *P<0.05, **P<0.01 and ***P<0.001, compared to RWIS control (t-test).
prevented by daily preadministration of NSP, 50, 100 and 150 mg/kg/day, dose-dependently. When the mice were pretreated with 150 mg/kg/day of NSP, in particular, considerable preventive effects over 80% were observed in both the body and pyloric regions of the stomach. Also, the decrease in hepatic blood flow caused by exposure to RWIS was inhibited by daily pretreatment with NSP. However, the magnitude of these effects was smaller than that noted in the stomach. On the other hand, concerning the decrease in dermal blood flow, NSP failed to show preventive effects in the doses and schedule employed in the present study. In addition, little change was recognized in non-stressed mouse hepatic blood flow following continued treatment with NSP, 100 and 150 mg/kg/day, for 6 days (data not shown).

Figure 6 shows a schema of tissue blood flow changes in mice exposed to SART stress or RWIS and the preventive effect of NSP on them.

With respect to the tissue blood flow in SART-stressed mice, a decrease in the stomach, no change in the liver and an increase in the cutis were observed, and changes of both gastric and dermal blood flow were prevented almost to the normal level by consecutive administration of NSP. By contrast, RWIS-loaded mice uniformly revealed remarkable decreases in all tissue blood flows in the stomach, liver and cutis. The rate of the effect of NSP on these decreases differed according to the organ. In RWIS mouse stomach, NSP exhibited a great preventive effect on the blood flow decrease to the normal level, which was similar to that found in SART-stressed mice, whereas only a slight effect was obtained in the liver, and no effect was noted in the cutis.

3) Changes in the tissue blood flow of SART-stressed mice caused by cervical vagotomy or chemical sympathectomy: Figure 7 shows blood flow changes in non-stressed mice after left-cervical vagotomy and sympathetic chemical denervation produced by 6-OH-DA.

Both vagotomy and the single administration of 6-OH-DA, 50 or 100 mg/kg, caused significant decreases in gastric blood flow. However, hepatic blood flow was not significantly affected by any treatment. On the other hand, in the cutis, 5 mg/kg of 6-OH-DA tended to increase the dermal blood flow, and relatively larger doses, 50 and 100 mg/kg, elicited significant increases in blood flow in both the shoulder and lumbar region to about 130% of the control values, although vagotomy resulted in no change.

Figure 8 indicates the correlation between vagotomy as well as sympathetic chemical denervation and SART stress, as compared to the data obtained from non-stressed mice.

As seen in Fig. 8, gastric blood flow was reduced by vagotomy alone almost to the SART-stressed control flow level. When SART stress was loaded after vagotomy, the rate of the blood flow decrease was not more
than that elicited by vagotomy alone. In other words, the gastric blood flow for vagotomized mice showed no difference between non-stressed and SART-stressed groups, and the gastric blood flow decrease caused by SART stress was prevented by cervical vagotomy.

The gastric blood flow values in SART-stressed mice which were treated with 5 mg/kg/2 days x 3 of 6-OH-DA for the period of SART stressing were similar to SART-stressed control values. In other words, in this case, no significant influence was recognized on gastric blood flow in SART-stressed mice as

---

**Fig. 7.** Influences of vagotomy and sympathetic chemical denervation on tissue blood flow in non-stressed mice. No. of mice: 5–15/treated group and 17–25/control group. *P<0.05, **P<0.01 and ***P<0.001, compared to the control, and $P<0.05$ and $^*$P<0.001, compared to the sham-operated group (t-test). a) measured on the day following the last treatment of 5 mg/kg/2 days x 3 times, b) measured 2–3 hr after a single administration of 50 or 100 mg/kg.

**Fig. 8.** Influences of vagotomy and sympathetic chemical denervation on tissue blood flow in SART-stressed mice. □: Non-stress (N) and ■: SART stress (S). No. of mice: 5–15/treated group and 7–13/SART-stressed control group. *P<0.05, **P<0.01 and ***P<0.001, compared to the respective non-stressed values (t-test).
well as in non-stressed mice. On the other hand, when SART-stressed mice received a single administration of 100 mg/kg of 6-OH-DA, the gastric blood flow reduced by SART-stress loading showed a tendency of greater decrease. 

As no flow change was found in SART-stressed mouse liver, experiments like those mentioned above regarding hepatic blood flow were not carried out.

With respect to dermal blood flow, vagotomy failed to alter the tissue blood flow in SART-stressed mice as well as in non-stressed mice. On the contrary, when 6-OH-DA was administered to SART-stressed mice, the dermal blood flow augmented by SART-stress loading tended to show a further increase.

A schema of the above-described results concerning the influences of SART stress, vagotomy and sympathetic chemical denervation on tissue blood flow in mice and the correlation between them is shown in Fig. 9.

Fig. 9. Schema of tissue blood flow changes in mice caused by SART stress, vagotomy and sympathetic chemical denervation. The marks, †, ‡ and †, ‡, indicate the direction and the rate of changes in blood flow. ↔, → and ←: No change.

Discussion

When animals are exposed to various types of stimulation such as hypoxia, simple thermal stimulation and so forth, the blood flow shows inversed changes generally between the external surface and internal organs. Such a phenomenon has been widely known for a long time as the so-called “law of Dastre and Morat” (22). In this study, likewise, an increase in dermal blood flow and a decrease in gastric blood flow were observed in mice subjected to SART stress. However, it has also been reported that SART-stressed mice have increased blood flow in the abdominal aorta and superior mesenteric artery in contrast with a decrease in the common carotid artery. Therefore, it is apparent that considerably complicated changes probably occur in the systemic blood flow regulatory system in this stressed state.

It is well-known that hepatic blood flow is abolished in the common stressed state (23), whereas little flow change was observed in SART-stressed mouse liver in the present study.

Our consideration was focused on the relationship between these tissue blood flow changes and autonomic tone.

It has been reported by Bell and Battersby...
that vagotomy causes a decrease in gastric mucosal blood flow. A decrease in submucosal blood flow after vagotomy has also been demonstrated by Mackie and Turner (25). These observations are consistent with our findings that vagotomy elicited a decrease in gastric blood flow in the subserous region, although the regions in which blood flow was estimated, differed from each other.

The gastric blood flow in the vagotomized plus SART-stressed mice was similar to that in the mice treated with vagotomy alone, and so it follows that SART stress failed to cause a decrease in gastric blood flow in vagotomized mice. These results raise the possibility that the gastric blood flow decrease observed in SART-stressed mice may be at least partly associated with a decrease in the tension of the parasympathetic nerve. In addition, from the fact that the influence of SART-stress loading did not appear in vagotomized mice, it is supposed that the peripheral changes occurring in SART-stressed animals may be under the control of the higher parasympathetic center.

On the other hand, the findings in SART-stressed mice following 6-OH-DA treatment suggest that the gastric blood flow decrease caused by SART stress may be essentially different in its mechanism from that due to 6-OH-DA.

Accordingly, it is considered that SART-stressed mice are in a sympathicotonic state in the stomach, which results from a decrease in parasympathetic tone rather than an increase in sympathetic tone.

Dermal blood flow is well-known to be principally regulated by the sympathetic nervous system. In this study, an increase in dermal blood flow was shown in mice treated with 6-OH-DA, an adrenergic degenerator. Similarly, it has been reported in humans that dermal blood flow approximately doubles following sympathetic blockade (26). The results obtained from SART-stressed mice receiving 6-OH-DA, however, suggest that the SART stress-induced increase may be different from 6-OH-DA-induced increase in its mechanism. In other words, the possibility cannot be excluded that the dermal blood flow increase observed in SART-stressed mice may be associated with factors other than the adrenergic nerve such as the sympathetic, cholinergic vasodilator nerve.

In conclusion, it is likely that greater changes in the activities of the autonomic, cholinergic nervous systems may occur in both SART-stressed mouse stomach and cutis. The findings that the tissue blood flow changes in the mice with 6-OH-DA-induced systemic suppression of the sympathetic nervous system corresponded to those of SART-stressed mice are thought to support our previous conclusion that SART-stressed animals can probably be regarded as autonomically imbalanced vagotonic-type animals from the viewpoint of their systemic symptoms, from the results of application to experimental animals of the testing methods used clinically for examining autonomic nervous function (3).

There are many reports concerning the decrease of gastric blood flow in RWIS-loaded mice (27). It is generally thought that the excitement of the sympathetic nerves occurs at least in the beginning of the process of stress as a first step, which results in blood flow decrease. In our present study, gastric, hepatic and dermal blood flows uniformly decreased in RWIS-loaded mice. In mice exposed to such severe acute stress as RWIS, therefore, only the first step is thought to be manifested. On the other hand, as SART stress is subacute, differential autonomic tensions in individual organs may occur as a second step.

Our attentions were finally directed to the action of NSP, a sedative analgesic. NSP has been reported to have protecting effects against various anomalies such as hypotension (5), abnormal ECG (6), etc. observed in SART-stressed animals, and it has been reported to be also effective on the stress ulcer (28) in RWIS animals. In the present study, NSP showed protective effects to the normal level on both the decrease in gastric blood flow and the increase in dermal blood flow in SART-stressed mice. These effects on both the decrease and increase are thought to confirm that NSP is effective in moderating the symptoms induced by SART stress, a model symptom for dysautonomia. In RWIS mice, NSP showed
inhibitory effects also on the decrease in the gastric and hepatic, especially gastric blood flow, showing no effects on the decrease in dermal blood flow. Namely, NSP was found to inhibit the increase or decrease in tissue blood flow in both mice subjected to the SART stress and those subjected to RWIS, these inhibitory effects being rather larger in SART-stressed mice than in RWIS mice. These observations suggest that NSP has a regulating or modulating action on the autonomic abnormality.

References

1. Kita, T., Hata, T., Yoneda, R. and Okage, T.: Stress state caused by alternation of rhythm in environmental temperature, and the functional disorders in mice and rats. Folia Pharmacol. Japon. 71, 195–210 (1975) (Abs. in English)
2. Hata, T., Kita, T., Itoh, E. and Harada, N.: Experimental studies on optimal conditions of loading SART stress (repeated cold stress) upon animals. Japan. J. Psychosom. Med. 24, 257–266 (1984)
3. Kita, T., Hata, T., Itoh, E. and Namimatsu, A.: Testing methods for vegetative syndrome in the rat and effects of Neurotropin and other drugs. Japan. J. Psychosom. Med. 23, 61–68 (1983)
4. Kita, T., Hata, T., Iida, J., Yoneda, R. and Ishida, S.: Decrease in pain threshold in SART stressed mice. Japan. J. Pharmacol. 29, 479–482 (1979)
5. Hata, T., Kita, T., Namimatsu, A., Itoh, E. and Oda, Y.: Changes of blood pressure and regional blood flow in SART rats and drug actions on these changes. Folia Pharmacol. Japon. 79, 335–342 (1982) (Abs. in English)
6. Hata, T., Kita, T., Itoh, E. and Namimatsu, A.: Changes of the function in the heart of SART stressed (repeated cold stressed) mice and the action of Neurotropin on these changes. Folia Pharmacol. Japon. 79, 487–492 (1982) (Abs. in English)
7. Hata, T., Nishida, S., Kita, T., Itoh, E. and Harada, N.: Change of the immune response in SART stressed animals and influences of some drugs on it. Shinshin-Igaku 24, 301–308 (1984) (Abs. in English)
8. Yoneda, R., Sugahara, K., Kita, T., Hata, T., Iida, J., Ishida, S. and Ohba, Y.: Organ weights and hematological observation in SART stressed rats or mice, and effects of extracts isolated from vaccinia virus inoculated and inflamed skin of rabbits (Neurotropin®). Pharmacometrics 18, 587–596 (1979) (Abs. in English)
9. Kita, T., Hata, T., Itoh, E. and Harada, N.: Methacholine- and adrenaline-induced arrhythmias in repeatedly cold-stressed mice. Japan. J. Pharmacol. 35, 327–329 (1984)
10. Aukland, K., Bower, B.F. and Berliner, R.W.: Measurement of local blood flow with hydrogen gas. Circ. Res. 14, 164–187 (1964)
11. Yoneda, R., Kita, T., Hata, T. and Namimatsu, A.: Experimental partial sympathicotonia, and effects of some drugs on it in restraint and water immersion stressed animals. J. Pharmacobiodyn. 3, 692–701 (1980)
12. Yoneda, R., Hata, T., Kita, T., Namimatsu, A. and Itoh, E.: Experimental pharmacological study on partial sympathicotonia in restraint and water immersion stressed animals. J. Pharmacobiodyn. 4, 251–261 (1981)
13. Kita, T., Hata, T., Harada, N. and Itoh, E.: An abnormal ECG and the adrenaline-induced arrhythmias in restraint and water immersion stressed mice and effects of oxprenolol on them. Folia Pharmacol. Japon. 83, 373–382 (1984) (Abs. in English)
14. Kita, T., Hata, T., Iida, J. and Ishida, S.: Decrease of ACh response in isolated duodenum from SART stressed (repeated cold stressed) mice. Folia Pharmacol. Japon. 75, 33–44 (1979) (Abs. in English)
15. Hata, T., Kita, T., Iida, J., Yoshida, H., Uchida, S. and Ishida, S.: Decrease of ACh response in isolated duodenum from repeated cold stressed (SART stressed) mice. J. Pharmacobiodyn. 1, 338–340 (1978)
16. Uchida, S., Takeyasu, K., Noguchi, Y., Yoshida, H., Hata, T. and Kita, T.: Decrease in muscarinic acetylcholine receptors in the small intestine of mice subjected to repeated cold stress. Life Sci. 22, 2197–2204 (1978)
17. Hoedt-Rasmussen, K.: Regional cerebral blood flow. Acta Neurol. Scand. 43, 1–79 (1967)
18. Porter, C.C., Totaro, J.A. and Stone, C.A.: Effect of 6-hydroxydopamine and some other compounds on the concentration of norepinephrine in the hearts of mice. J. Pharmacol. Exp. Ther. 140, 308–315 (1963)
19. Goldman, H. and Jacobowitz, D.: Correlation of norepinephrine content with observations of adrenergic nerves after a single dose of 6-hydroxydopamine in the rat. J. Pharmacol. Exp. Ther. 170, 119–133 (1971)
20. Krishnamurty, V.S.R. and Grollman, A.: Contractile response of rat aorta to norepinephrine and tyramine. J. Pharmacol. Exp. Ther. 182, 264–272 (1972)
21. Westfall, D.P.: The effects of denervation.
Tissue Blood Flow in Stressed Mice

22 Iriki, M.: Regional differentiation of sympathetic efferents evoked by thermal, hypoxic and other stimulations. J. Physiol. Soc. Japan 45, 181–199 (1983) (in Japanese)

23 Namiki, M. and Sekiya, C.: Experimental approach to stress—physiologically. Igaku No Ayumi 125, 338–345 (1983) (in Japanese)

24 Bell, P.R.F. and Battersby, A.C.: Effect of vagotomy on gastric mucosal blood flow. Gastroenterology 54, 1032–1037 (1968)

25 Mackie, D.B. and Turner, M.D.: Vagotomy and submucosal blood flow. Arch. Surg. 102, 626–629 (1971)

26 Folkow, B. and Neil, E.: Circulation, p. 397. Oxford University Press, Inc., London (1971)

27 Hatta, S.: Experimental studies on the role of the autonomic nervous system in stress ulcer—mainly on the measurement of gastric blood flow and gastric motility. J. Japan. Practical Surg. Soc. 82, 1212–1223 (1981) (Abs. in English)

28 Hata, T., Kita, T. and Yoneda, R.: Central activity, antihypertensive action and antiulcerogenic effects of Neurotropin. Folia Pharmacol. Japon. 72, 879–890 (1976) (Abs. in English)