EXPERIMENTAL PARTIAL SYMPATHICOTONIA, AND EFFECTS OF SOME DRUGS ON IT IN RESTRAINT AND WATER IMMERSION STRESSED ANIMALS

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The contractile response to acetylcholine (ACh) of the isolated duodenum from the restraint and water immersion stressed (RWIS) mouse was found to be enhanced by the stress for 1 hr and reach a maximum in 3 hr stress followed by a decrease. It was clarified that this rise in the response is not due to the change in the affinity to ACh but due to the increase of the intrinsic activity. The contractile response to KCl was augmented only when concentration of KCl was high, while the response to BaCl
was little enhanced in the stressed animal.

The relaxing response to noradrenaline (NA) of the isolated duodenum from rat, on the other hand, was reduced by the stress. Such reduced response to NA was observed to be more marked than the enhanced response to ACh in the vas deferens isolated from the stressed animal.

The pretreatment to the RWIS mouse with either antiadrenergic or cholinergic drugs resulted in the clear-cut blockade of the enhancement of response to ACh of the isolated duodenum from this animal. These results contrasted to the effects on the reduced response to ACh of the isolated duodenum from the SART stressed (repeated cold stressed) mouse. The pre-administration of psychotropic drugs showed marked suppression on the enhancement of response of the duodenum of the RWIS animal, though there was a quantitative difference between the RWIS and SART animals. The pretreatment with a neurosedative, Neurotropin® (NSP) was also found to show similarly marked suppressive action.

From these results, it was considered that the duodenum and the vas deferens of the RWIS animal are in the state of the sympathicotonia, namely partial sympathicotonia.

Keywords — sympathicotonia; stress; water immersion stress; restraint stress; small intestine; vas deferens; vagotonia

INTRODUCTION

We have previously reported[1-6] that the symptoms of the mouse and rat which are loaded with repeated cold stress, the specific stress caused by alternation of rhythm in temperature (SART), are in the specific pathological diseased state which is distinct from the symptom observed in non-specifically stressed animals. In particular, on the basis of the markedly reduced contractile responsiveness[7] of isolated duodenum to acetylcholine (ACh), and the effect of drugs[8] on this lowered response or the outcome of the vagotomy,[9] we have been considering that the SART stressed animal is in the state of partial vagotonia. From a biochemical-pharmacological point of view, the quantitative reduction,[10] but not qualitative change, in the ACh receptor has been also reported by Yoshida et al. in the SART stressed animal with partial vagotonia.

It is also conceivable, however, that the symptom which is contrary to the specific pathological disease observed in the SART stressed animal could develop in the body. Therefore, we have chosen the restraint and water immersion stress (RWIS) as an acute stress which is completely different from the SART stress, and investigated the reactivities to drugs of isolated duodenum or isolated vas deferens from the
RWIS stressed animal. The results thus obtained are reported below.

MATERIALS AND METHODS

Male mice of the ddY strain weighing 20—23g and male rats of the Wistar strain weighing 200—300g were used. The mouse was fasted for more than 18 hr, then restrained in a wire cloth cylinder and immersed in 15° water vertically and up to a depth of the xiphoid process for 3 hr according to the method of Watanabe et al. 11) The rat was fixed on the back and immersed in 25° water for 20 hr by the method of Takagi et al. 12)

The RWIS mouse and rat were decapitated, and the duodenum or the vas deferens was dissected out. A piece of the duodenum was isolated from about 5 mm distal to the gastric pylorus for a length of about 20 mm. The entire length of the vas deferens, namely, from the seminal vesicle end to the testis, was isolated. Each of these isolated organ specimens was suspended vertically in a organ bath filled with 20 ml of Tyrode medium at 32° and bubbled with air, and the isotonic contraction or relaxation was recorded on a smoked paper on a kymograph. The tension was approx. 500mg in mouse duodenum, approx. 1g in rat duodenum, approx. 300mg in mouse vas deferens and approx. 400mg in rat vas deferens. The mean value of maximum response caused by each drug in the duodenum or the vas deferens isolated from normal mice was set at 100, and the percent response was calculated on other concentration of the drug or other experiments.

The drugs used for testing the reactivity of the tissue specimen were ACh (Daiichi, Ovisor®), noradrenaline (NA, Sankyo, Norepinephrine®), KCl and BaCl₂. Other drugs pre-administered to animals were NA; α-methyldopa (Nippon Merck-Banyu, Aldomet®), guanethidine sulfate (Takeda-Ciba, Ismeline®); ACh, neostigmine (Sigma); atropine sulfate (Wako); reserpine, chlorpromazine hydrochloride (Shionogi); carpine hydrochloride (Yoshitomi, Defektor®), diazepam (Takeda, Cercine®); and Neurotropin® (NSP, Nippon Zoki, 5 times concentrated than the commercial product). Water soluble drugs were dissolved in physiological saline, and insoluble ones were suspended in 2% gummi arabicum solution.

Statistical significance was calculated by Student’s t test.

RESULTS

1. Time Course of the Change of the Reactivity to ACh of the Duodenum isolated from the RWIS Mouse

The time course of the change of the reactivity to ACh of the duodenum isolated from the RWIS loaded mouse is shown in Fig. 1, and the reactivity

![Graph showing the influence of restraint and water immersion on ACh-response of duodenum isolated from stressed mice.](image-url)

FIG. 1. Influence of Restraint and Water Immersion Stress on ACh-response of Duodenum isolated from Stressed Mice

The ordinate scale shows the % contraction compared with the mean value of contraction caused by 5.5×10⁻⁴ M of ACh in the isolated normal mouse duodenum. Mice were fasted for 18 hr before restraint and water immersion. Results are mean values (± S.E.) for groups of 10—18 mice. Statistical difference: *: p<0.05, **: p<0.01, ***: p<0.001 compared with normal.

- restraint and water immersion for 3 hr.
- restraint and water immersion for 2 hr.
- restraint and water immersion for 1 hr.
- restraint and water immersion for 4 hr.
- restraint and water immersion for 5 hr.
- normal.
of the duodenum isolated from fasted mouse or from restrained mouse is given in Fig. 2.

As shown in Fig. 1, in the case of the RWIS mouse, the response to ACh began to be enhanced by the restraint and water immersion for 1 hr, and the increase became statistically significant ($p < 0.01 - 0.001$) in the case of 2–3 hr immersion, compared with normal mice. In particular, this increase was most remarkable when the immersion was made for 3 hr, and the increase by more than 50% ($p < 0.001$) compared with the normal mouse, was observed at $10^{-4} - 10^{-3}$ M of ACh. Water immersion for 4–5 hr resulted in a smaller enhancement of the reactivity.

As shown in Fig. 2, both the duodenum isolated from the mouse fasted for 21 hr and that from the mouse restrained for 3 hr after 18 hr fasting showed similar reactivities to ACh, thus no statistical differences were observed in the dose-response curve between these stressed mice and the normal mouse.

According to these results, it may be considered that the enhancement of the reactivity to ACh of isolated duodenum from the RWIS mouse is caused by placing the animal under the strongly stressed condition of water immersion with restraint. Therefore, it was decided to stress the animal by restraint and water immersion for 3 hr after 18 hr fasting for subsequent experiments.

2. Changes in the Reactivities to ACh, KCl, BaCl$_2$ and NA of the RWIS Mouse Duodenum

Fig. 3A shows the dose-response curves for the contraction caused by ACh of the duodenum isolated from the mouse loaded with RWIS for 3 hr, and the logarithmic transformation of the dose-response curve on the axes of log $x$ and log...

**FIG. 2.** Influence of Fasting or Restraint on ACh-response of the Isolated Mouse Duodenum

The ordinate scale is the same as shown in Fig. 1. Results are the mean values ($\pm$ S.E.) for groups of 7–10 mice.
- $\bigcirc$ normal.
- $\times$ fasting for 21 hr.
- $\bullet$ restraint for 3 hr after fasting for 18 hr.

**FIG. 3.** ACh-response in the Duodenum isolated from Restraint and Water Immersion Stressed Mice

The ordinate scale in Fig. 3A is the same as shown in Fig. 1. Results are mean values ($\pm$ S.E.) for groups of 10 mice. Statistical difference: **: $p < 0.01$, ***: $p < 0.001$ compared with normal.

Fig. 3B shows the logarithmic transformations of the dose-response curves in Fig. 3A.
- $\bigcirc$ normal.
- $\bullet$ stressed for 3 hr.
\(\frac{y}{(y_{\text{max}} - y)}\) is shown in Fig. 3B.

In Fig. 3A, the contraction of the RWIS mouse duodenum caused by about \(2 \times 10^{-6}\) M of ACh was nearly the same as the maximal contraction of the normal mouse duodenum caused by \(10^{-4} - 10^{-3}\) M of ACh, and the \% contraction by \(5.5 \times 10^{-4}\) M of ACh was about 50\% higher in the RWIS mouse duodenum than in normal mouse duodenum.

In Fig. 3B, there is no difference between the line obtained with the RWIS mouse and that with the normal mouse, thus the intersections on the x-axis, indicating the 50\% contraction level, are near \(5 \times 10^{-7}\) M for both lines.

The reactivities of the RWIS mouse duodenum to KCl and BaCl\(_2\) are shown in Fig. 4.

In Fig. 4A, the response to KCl of the RWIS mouse duodenum was significantly \((p < 0.05)\) greater than that of the normal duodenum when the concentration of KCl was higher than \(4 \times 10^{-2}\) M. In the case of BaCl\(_2\) which is known to directly act on intestinal smooth muscle, the reactivity of the RWIS mouse duodenum was found to be slightly enhanced as shown in Fig. 4B.

The logarithmic transformations of these dose-response curves, using the axes of log x and log \(\frac{y}{(y_{\text{max}} - y)}\), are inserted in the left upper corner of each graph of Fig. 4. Any shift between the curves for the normal and RWIS mice was not observed in the case of either KCl or BaCl\(_2\).

The relaxing response to NA of the duodenum is shown in Fig. 5. As the duodenum from the

**FIG. 4.** KCl- and BaCl\(_2\)-response in the Duodenum isolated from Restraint and Water Immersion Stressed Mice

The ordinate scale shows the \% contraction compared with the mean value of contraction caused by \(6.7 \times 10^{-2}\) M of KCl in Fig. 4A and that by \(4.8 \times 10^{-2}\) M of BaCl\(_2\) in Fig. 4B, respectively, in the isolated normal mouse duodenum. Results are mean values (± S.E.) for groups of 3–7 mice. Statistical difference is compared with normal. Statistical difference: *: \(p < 0.05\).

○ ○ ○ normal.

● ● ● stressed for 3 hr.
mouse was not so sensitive to NA, the duodenum from the rat was used in this series of experiments. As shown in Fig. 5, the relaxation by NA of the RWIS rat duodenum was significantly ($p<0.01$) decreased in comparison with that of the normal rat. Although it is not shown in the figure, the contraction by ACh of the RWIS rat duodenum was also markedly enhanced in a manner similar to that with the RWIS mouse.

In order to further confirm the above possibility, the vas deferens, which is known to be predominantly controlled by the sympathetic nervous system, was used for subsequent experiments.

3. Changes in the Reactivities of the Vas Deferens isolated from the RWIS Animal to NA and ACh

As shown in Fig. 6, the vas deferens from the RWIS mouse showed a marked reduction in the reactivity to NA, while an enhanced reactivity to ACh. Similarly, though not shown in the figure, the vas deferens of the RWIS rat also showed a reduction in the reactivity to NA and a rise in the response to ACh.

4. Effects of Some Drugs on the Change of the Response to ACh of the RWIS Mouse Duodenum

A drug was intraperitoneally administered to the mouse twice, 18 hr before and immediately before RWIS, and the reactivity to ACh was examined with the isolated duodenum. The response to ACh was measured at the concentration of $5.5 \times 10^{-7}$ M of ACh which was nearly equivalent to the ED$_{50}$ value estimated by Fig. 3. The mean height of contractions induced by $5.5 \times 10^{-7}$ M of ACh in the normal control mouse duodenum was set at 100, and the percent contraction of the duodenum of experimental mouse relative to that of normal mouse duodenum was calculated.

a) Effects of Autonomic Drugs — The results obtained by pretreatments with adrenergic, anti-
adrenergic, cholinergic and anticholinergic drugs are shown in Fig. 7.

From results shown in Fig. 7, the % contraction caused by $5.5 \times 10^{-7}$ M of ACh of the RWIS mouse duodenum was 157% compared with normal. The pre-administrations of α-methyldopa, 20 and 40 mg/kg; guanethidine, 5 and 10 mg/kg; ACh, 10 and 20 mg/kg, or neostigumine, 0.1 and 0.3 mg/kg, showed the dose-dependent suppressions of the enhancement of response to ACh of the isolated duodenum, and the response was near the normal level ($p < 0.05 - 0.001$). The pre-administration of either NA or atropine showed little effects. These results, therefore, indicate that the enhancement of response to ACh of the RWIS mouse duodenum was blocked by either the antiadrenergic drug or the cholinergic drug.

b) Effects of Psychotropic Drugs — The results obtained by the pre-administration of psychotropic drugs are shown in Fig. 8.

As shown in Fig. 8, the pre-administration of major tranquilizers such as reserpine, 1 mg/kg, chlorpromazine, 1 mg/kg, or carpipramine, 10 mg/kg, significantly ($p < 0.05 - 0.01$) suppressed the enhancement of response to ACh by the stress, and the response was near the normal level. The pre-administration of a minor tranquilizer, diazepam, 2-5 mg/kg, was also found to suppress the enhancement. Moreover, the pre-administration of a neurosedative, NSP, 12.5-25.0 ml/kg,

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**FIG. 6. Noradrenaline and ACh-response in Isolated Vas Deferens from Restraint and Water Immersion Stressed Mice**

The ordinate scale shows the % contraction compared with the mean value of contractions caused by $3 \times 10^{-4}$ M of NA or that by $3 \times 10^{-5}$ M of ACh, respectively, in the isolated normal mouse vas deferens. Results are mean values ($\pm$ S.E.) for groups of 7-10 mice. Statistical difference: *: $p < 0.05$, **: $p < 0.01$ compared with normal.

- O — O normal.
- • ---- • stressed for 3 hr.
FIG. 7. Effects of Autonomic Drugs on ACh-response in the Duodenum isolated from Restraint and Water Immersion Stressed Mice

Results are mean values (± S.E.) for the drug administered groups of 5—7 mice. Statistical difference: *: p< 0.05, **: p< 0.01, ***: p< 0.001 compared with stressed control.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drugs and dose (mg/kg × 2)</th>
<th>% contraction by ACh (mean±S.E.)</th>
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<td>0</td>
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<tr>
<td>Normal</td>
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<tr>
<td>Stressed</td>
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<tr>
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<tr>
<td>Stressed + α-methyldopa 40</td>
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<tr>
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<td>Stressed + guanethidine 10</td>
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<tr>
<td>Stressed + ACh 10</td>
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<tr>
<td>Stressed + ACh 20</td>
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<td>Stressed + neostigmine 0.3</td>
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<tr>
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<tr>
<td>Stressed + atropine 0.5</td>
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FIG. 8. Effects of Psychotropic Drugs and Neurotropin on ACh-response in the Duodenum isolated from Restraint and Water Immersion Stressed Mice

Results are mean values (± S.E.) for the drug administered groups of 5—7 mice. Statistical difference: *: p< 0.05, **: p< 0.01, compared with stressed control. a): ml/kg.
resulted in a dose-dependent and significant ($p < 0.05-0.01$) suppression of the enhancement. 5. Comparison of the Effects of Various Drugs on the Response to ACh between the Duodenums isolated from RWIS and the Duodenum from SART Stressed Mice

The effects of pre-administered drugs on the enhancement of response to ACh of the RWIS mouse duodenum are compared with those on the reduction of response to ACh of the SART mouse duodenum as shown in Table I.

As seen in Table I, the adrenergic drug, NA, and the muscarinic blocker, atropine, which were both effective on the reduction of response to ACh in the SART stressed mouse duodenum, were ineffective in enhancing a response to ACh in the RWIS mouse duodenum. On the other hand, the adrenergic blockers such as α-methyldopa and guanethidine and the cholinergic drugs such as ACh and neostigmine, which had no effect on the SART stressed mouse duodenum, were now found to be effective on the RWIS mouse duodenum.

Thus, there was an inverted correlation between the effect of drugs on the RWIS mouse duodenum and that on the SART mouse duodenum.

Psychoactive drugs showed an inhibiting action on both the enhancement of response to ACh in the RWIS mouse and the reduction of response to ACh in the SART mouse, though there were some quantitative differences. A neurosedative, NSP, was found to be effective on the response to ACh both in the RWIS mouse and in the SART mouse.

DISCUSSION

It has been our understanding that the SART stressed animal is in the state of pathological disease with partial vagotonia in view of the pharmacological analysis of the effect of autonomic drugs on the reduction of response to ACh of the isolated duodenum, the disappearance of such reduction by vagotomy, and the quantitative decrease of ACh receptors in the duodenum. However, it is conceivable that abnormality in the autonomic nervous system can, also, produce a pathological diseased state which is rather con-

<table>
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<tr>
<th>Drugs</th>
<th>Dose (mg/kg)</th>
<th>ACh-response</th>
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Drugs were administered i.p. to mice, twice before restraint and water immersion stress, and once daily × 5 for SART stressing. *: ml/kg. The mark, ↓, indicates the inhibiting effect of drugs on the enhancement of response to ACh of the RWIS mouse duodenum, the mark, ↑, indicates the inhibiting effect of drugs on the reduction of response to ACh of the SART mouse duodenum, and the mark, --, means the lack of any effect. ↓↓ > ↓↓ > ↓↓ > ↓↓.
trary to the vagotonia. In order to prove this possibility, we have selected the acute stress, RWIS, which is different from a chronic repeated stress such as the SART stress, and the responses to drugs of the isolated duodenum and vas deferens were examined in the present study.

The results indicated that the contractile response to ACh of the isolated mouse duodenum was markedly augmented by RWIS for 3 hr, and that the stress for 4–5 hr rather reduced the extent of such augmentation. The loading only with either fasting or restraint stress did not produce the augmentation of the response to ACh. It was thus clarified that the enhancement of the response to ACh of the duodenum may occur under the strongly stressed condition such as water immersion with restraint, and it takes places at a relatively early stage after the loading with RWIS. It was also observed that this rise in the response to ACh is associated with the rise in the intrinsic activity, but not with the change of the affinity. In the case of KCl and BaCl₂, also, a steady affinity and rise in intrinsic activity were observed.

From the findings that the extent of the rise in the intrinsic activity was most remarkable in the case of the response to ACh, moderate with KCl, and slight with BaCl₂, the element for the muscle contraction itself appears not to be damaged in the stressed animal, though the involvement of Ca²⁺ ions in the contractile mechanism of the smooth muscle should be taken into consideration.

The relaxation of the isolated rat duodenum by NA, on the contrary to ACh, was found to be reduced by the stress.

From these findings, the RWIS animal may be considered to be in the state of excessive partial sympathicotonia. In order to further confirm this possibility the vas deferens, which is known to have greater sympathetic reactivity than the duodenum, was used. The vas deferens from the RWIS mouse and rat showed greater lowering of the contractile response to NA compared with the extent of the augmentation of the contractile response to ACh. Moreover, the enhancement of response to ACh of the isolated mouse duodenum was blocked by the pretreatment with anti-adrenergic and cholinergic drugs, while the pretreatment with adrenergic and anticholinergic drugs did not block the enhancement of response at all. Based on the above results, the RWIS animal is thought to be in the state of excessive sympathicotonia at least in the duodenum and the vas deferens. The effect of pre-administered autonomic drugs on the RWIS mouse was found to be completely opposite to that on the SART stressed mouse. This finding is considered to support the concept further that the RWIS animal is in the state of partial sympathicotonia, while the SART stressed animal is in the state of partial vagotonia.

In case of the pretreatment of psychotropic drugs, either the major or minor tranquilizers inhibited the change of response to ACh both in the RWIS and the SART animals. Among these drugs, reserpine, chlorpromazine and carpipramine are known to be associated with the release, uptake and storage of NA in the adrenergic nerve ending. However, in the present case, these major tranquilizers are thought to improve secondarily the unbalance between the sympathetic and parasympathetic nervous systems by acting on the central nervous system.

The finding that a neurosedative, NSP, suppressed not only the reduction of response to ACh of the SART mouse duodenum but also the enhancement of response to ACh of the RWIS mouse duodenum might be related to the known clinical effect of this drug, namely the effectiveness on abnormally excited nervous system.

Since the loading of RWIS to the mouse and rat produces the ulcer-like symptom in the gastric mucosa, the RWIS animal has been used as one of the model of experimental ulcer. Experimental gastric ulcer can be produced also in the animal whose pituitary or adrenal is removed, but such ulcer formation has been reported not to occur in the vagotomized animal. On the basis of these facts, the generation of gastric ulcer has been thought to be largely due to the excitation of the parasympathetic nervous system. In
addition to this, the spasm of blood vessels in gastric mucosa induced by the stress loading and also the participation of the sympathetic nervous system\textsuperscript{19,20} have been considered to be the cause of gastric ulcer.

As reported in the present paper, we have carried out experiments with the duodenum and vas deferens isolated from the RWIS loaded animal, and were able to obtain the results suggesting the existence of autonomic imbalance in this animal, namely at least in the duodenum and the vas deferens there exists peripheral sympathetic tonia. Attempts of applying the adrenalectomy, vagotomy or sympathectomy to the experimental animal are in progress, and the investigation on the cause of the altered responsiveness to drugs of the duodenum isolated from the RWIS animal is also being carried out.

REFERENCES