EFFECTS OF RESERPINE AND ADRENALINE ON THE SINOATRIAL NOTCHED POTENTIAL IN RABBIT

NOBORU TODA

Department of Pharmacology, Faculty of Medicine, Kyoto University, Kyoto

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In the course of studies in this laboratory on the mode of action of catecholamines on the transmembrane potential of the extirpated atrium of rabbit (1), some of the potentials recorded from the pacemaker area (West) responded differently to reserpine and adrenaline from the typical pacemaker potentials. The potential under this study was recorded from the area which was somewhat wider than the triangular pacemaker area shown schematically by West (2). This potential was characteristic in a notching of the upstroke and a slow rate of depolarization, and was very sensitive to reserpine and adrenaline. The notched potential in the sinoatrial node of rabbit's heart was at first reported by West (2), who studied the distribution of the potential. Although the similar notched potentials have been reported in the atrioventricular node of mammalian heart (3, 4), the smooth muscle of uterus (5) and the sinoauricular funnel of amphibian heart (6), the exact nature of the potentials remains to be settled. In the present report the responses of the notched potential recorded from the sinoatrial node of rabbit's heart were studied. It is expected that the responses of the potential to reserpine and adrenaline might have some contribution to elucidate the mechanism of the pacemaker activity.

METHODS

Albino rabbits, weighing 1.8 to 2.2 kg, were killed through haemorrhage by cutting of both common carotid arteries. The heart was extirpated and the right auricle was separated from the heart. Immediately thereafter, the auricle was fixed on the cork plate immersed in warm (30°C) and O₂-saturated modified Tyrode solution. The volume of the solution in the bath was 50 ml. The composition of the modified Tyrode solution is as follows: NaCl 8.6 g, KCl 0.2 g, CaCl₂ 0.2 g, MgCl₂ 0.05 g, NaH₂PO₄ 0.2 g, Na₂HPO₄ 1.6 g and glucose 1.0 g in 1000 ml. The preparation always showed a rhythmical automatic contraction for 8 to 14 hours.

A glass capillary tube filled with 3 molar KCl solution was used as a different electrode. As an indifferent electrode a platinum wire immersed in the nutrient solution of the bath was used. The potential changes of the single muscle fiber were recorded following the method of Matsumura and Takaori (7). The potential changes amplified through d.c. amplifier were photographed from a cathode-ray oscilloscope by use of a continuous recording camera. When it was required, the potentials were recorded by use of an ink-writing oscillograph.

All the drugs employed were administered into a side chamber connected with a main preparation chamber of the bath. The concentration of the drug in the bath was expressed as g/ml. Two and half milligram of reserpine dissolved in 1.0 ml of a mixture of propylene glycol (50 mg), phosphoric acid (2.0 mg), glucose (25 mg) and distilled water was used as a stock solution. pH of the reserpine solution was 2 to 3. None of the potential recorded was affected by the administration of the solvent less than 0.2 ml. As adrenaline hydrochloride only *l*-form was used.

RESULTS

1) The sinoatrial notched potential

An atypical transmembrane potential which was different from that of pacemaker was recorded several millimeters apart from the area where the pacemaker potential was recorded. The potential obtained from the vicinity of the pacemaker area was distinguished from the pacemaker and atrial non-pacemaker potentials in the points that the former potential showed a notching followed by a slow rate of depolarization. Moreover, the potential frequently showed a prepotential succeeded by a notching and by a rising phase of the action potential (Fig. 1B). The farther was the distance of the recording electrode from the pacemaker area, the less was the slope of the prepotential. Some of the notched potential obtained from the area several millimeters far from the pacemaker area showed the notched potential without an appearance of the prepotential, as shown in Fig. 1C. The height and duration of the notching, usually 5.8 to 20 mV and 14.5 to 34.9 msec, were subjected to a considerable variation. Consequently, this potential seemed to coincide

FIG. 1. Typical patterns of the pacemaker potential (A), the notched potential with a prepotential and a large notching (B), the notched potential with a small notching (C) and the atrial non-pacemaker potential (D).

TABLE 1. The magnitude of the action potential (ap), the diastolic potential (dp), the overshoot (os) and the total duration of the action potential (td) in the pacemaker*, the notched and the atrial non-pacemaker* potentials.

* Marshall, 1957(8)

	ap (mV)	dp (mV)	os (mV)	td (msec)	Notching	
					Height (msec)	Duration (mV)
Pacemaker potential*	66 ± 1.0	61 ± 0.67	5 ± 0.45	189 ± 8.1		
Non-pacemaker potential*	89 ± 0.89	73 ± 0.70	16 ± 0.45	135 ± 4.9		
Notched potential (N: 20)	86 ± 1.8	76 ± 2.0	10 ± 0.59	150 ± 3.0	6-20	15-55

with the description of the notched potential by West (2). Fig. 1B and 1C show typical pattern of the notched potentials with and without prepotential. In Table 1 the height and duration of the action potential, the magnitude of the diastolic potential and the overshoot in the record of the notched potential are compared with those of the pacemaker and atrial non-pacemaker potentials. The figure and table show the similarities of the notched and pacemaker potentials in the total duration of the action potential and in the depolarization velocity, but show considerable dissimilarities in the height of action potential and in the overshoot.

Fig. 2 is the schematic representation of the sinoatrial node of rabbit shown from the endocardial surface. From B area the typical pacemaker potential was usually obtained. The notched area where West has obtained the notched potential is the triangular part encircled with the dotted lines in Fig. 2. In this experiment the notched potential was also obtained from A and C areas. The demarcation of the notched area from the pacemaker area was usually not clear-cut and the dimension of the notched area was subjected to a considerable variation. The pacemaker area was incompletely surrounded by the notched area. The notched potential was never

FIG. 2. Schematic representation of the area where the pacemaker, notched and non-pacemaker potentials were recorded (see text).

obtained from D area in Fig. 2, where the atrial non-pacemaker potential was recorded. This area was easily differentiated from the pacemaker and notched area macroscopically. The transmembrane potential which lacked the prepotential and notching but differed from the atrial non-pacemaker potential in the total duration was sometimes obtained from the vicinity of the sinoatrial node. However, this potential responded to reserpine in a manner similar to the pacemaker or atrial non-pacemaker potential.

2) *Effects of reserpine on the pacemaker potential and on the notched potential*

The administration of 10^{-6} to 10^{-5} of reserpine in the bath gave rise to the following characteristic effects on the pacemaker and notched potentials. Marked effects of reserpine were observed especially on the notched potential. The rate of rhythm gradually decreased in all the pacemaker potential, the notched potential and the atrial non-pacemaker potential. The effects of reserpine on the pacemaker potential were almost the same as those reported previously (1). As shown in Fig. 3A and 3B, depression of the action potential, decrease of the slope of prepotential, increase of the total duration of the potential, minute diminution of the maximal diastolic potential, retardation of the depolarization velocity and unchanged threshold potential were the main effects. Increase of the total duration, depression of the magnitude of action potential and unchanged resting potential by the same concentration of reserpine were observed in the atrial non-

FIG. 3A. Effects of 10^{-5} of reserpine on the pacemaker potential. The arrows indicate the abortive depolarization (see text). The scale of vertical lines at right side of each tracing is 100 mV. Time scale: 1 sec. Scales are same in the following figures.

FIG. 3B. Effects of 10^{-5} of reserpine on the pacemaker potential. I: before, II: 15 minutes after, III: 25 minutes after.

pacemaker potential.

The notched potential also responded to reserpine in a manner similar to the pacemaker potential during an early stadium (for about 20 minutes). But the characteristic effects of reserpine on the notched potential appeared earlier than those on the pacemaker potential. Twenty to forty minutes after 10^{-5} of reserpine the spike potential was suddenly abolished from the notched area. Thereafter, only a minute trace of the electrical pattern was recorded. Fig. 4A and 4B show the results. This electrical pattern could be interpreted as the depressed notching which did not fire to the usual spike potential and was called *notch-potential* in this report. The typical *notch-potentials* are shown in Fig. 4B, 5B, 7G and 9. In some of the preparations the *notch-potential* and the notched

FIG. 4. Effects of 10^{-5} of reserpine on the notched potential. (B) is an enlarged figure of effects of reserpine at 25 minutes and 40 minutes after the administration. The abrupt disappearance of the spike potential and the appearance of the *notch-potential* were observed.

FIG. 5. Effects of 10^{-5} of reserpine on the notched potential. (B) is an enlargement from right half of the lower part of (A). A gradual diminution in the height of the *notch-potential* at 30, 50 and 85 minutes after the administration of reserpine.

FIG. 6. Comparison of the effects of 10^{-6} of reserpine on the pacemaker potential and the notched potential in reference to the non-pacemaker potential. (A) The notched potential and the *notch-potential* recorded from notched area in the course of reserpine action are shown in the upper tracing. Lower tracing shows the non-pacemaker potential recorded at the same time. (B) The pacemaker potential and the abortive depolarization (see text) are shown in the upper tracing. Lower tracing shows the non-pacemaker potential.

potential with depressed spike irregularly appeared before the full development of the *notch-potential*, as shown in Fig. 5A and 5B. When the *notch-potential* had appeared, both pacemaker and atrial non-pacemaker potentials were little affected irrespective of decrease of the frequency. The results are shown in Fig. 6. In the course of time after the administration of reserpine the magnitude and frequency of the *notch-potential* gradually decreased and at last the *notch-potential* disappeared in accordance with the disappearance of the pacemaker and atrial non-pacemaker potentials. In few of the preparations which had

not shown any sign of the notching before, the marked notching in the upstroke of the potential appeared in the course of reserpine action. On the contrary to the above-mentioned case, some of the notching decreased in height after reserpine.

TABLE 2. The measured values of each component of the notched potential affected by reserpine in Fig. 7. ap: the magnitude of the action potential. mdp: maximal diastolic potential. tp: threshold potential. os: overshoot. td: total duration of the action potential (tp-1 and tp-2: see text).

	ap (mV)	mdp (mV)	tp-1 (mV)	tp-2 (mV)	os (mV)	td (msec)	Notching	
							Height (mV)	Duration (msec)
A	85.0	75.9	64.7	55.5	9.1	148.9	8.9	55.0
B	78.0	74.9	64.7	52.4	3.1	161.8	7.3	62.6
C	75.1	72.0	61.6	43.1	3.1	189.3	6.1	72.5
D	65.7	73.4	64.2	43.1	—	208.4	6.1	84.0
E	27.5	68.8	64.2	43.1	—	213.9	5.5	87.7
F	—	64.2	64.2	—	—	—	4.6	120.7
G	—	64.2	64.2	—	—	—	4.6	120.7

The slope of prepotential of the notched potential decreased gradually before the manifestation of the *notch-potential*. After the manifestation of the *notch-potential*, the slope of prepotential disappeared, and the maximal diastolic potential decreased to the same level of the threshold potential. The threshold level of the notched potential with prepotential or the resting level of the notched potential without prepotential remained unchanged.

Fig. 7 shows the effects of 10^{-5} of reserpine on the notched potential at 10, 20, 30, 40, 45 and 50 minutes after the administration, respectively (B-G). Table 2 and Fig. 7

FIG. 7. Photographic representations of the changes of the notched potential in response to 10^{-5} of reserpine at 10, 20, 30, 40, 45 and 50 minutes after the administration respectively. (A) Before reserpine, (B-G) After reserpine, (H) Superimposed figure of potential changes.

show the changes of the magnitude of the action potential, the maximal diastolic potential, the overshoot, the total duration of action potential, and the duration and height of notching after the administration of 10^{-5} of reserpine. In the course of time after reserpine the duration of the potential from the rising phase to the end of the repolarization was prolonged. The magnitude of the action potential was gradually depressed and the action potential finally disappeared. But there remained the *notch-potential*. In Fig. 7 the action potential shows the spike potential with preceding prepotential and the notching before the administration of reserpine (A). Ten minutes after the administration of 10^{-5} of reserpine the action potential was depressed in magnitude (Fig. 7B). In the course of reserpine action, the action potential was further depressed in magnitude and there appeared another small notching immediately after the prolonged first notching (Fig. 7C). Further effects of reserpine were the flattening and the increase of the duration of the first notching and the further depression of the spike potential (Fig. 7D and 7E). At last, the duration of the depolarization phase was approximately equal to that of the repolarization phase. In Fig. 7F the spike potential completely disappeared and the *notch-potentials* were distinctly separated. The superimposed figure of the potential changes in the course of reserpine action is shown in Fig. 7H. If the notching of the notched potential is regarded as a constituent of the depolarization phase, the value of tp-1 in the figure of Table 2 shows the threshold of the notched potential. This value was hardly affected by reserpine. On the other hand, if the notching represents a local response to evoke the firing of the spike, the value of tp-2 in Table 2 shows the threshold, which was gradually decreased in the course of reserpine action. The marked effects of reserpine on the notched potential were at first the depression of the spike potential and the increase of the duration of the depolarization phase, and then the abolishment of the spike.

In the pacemaker potential the abortive small pattern of wave which did not fire to a usual spike potential was sometimes observed, when the rate of rhythm decreased after reserpine. This small pattern of wave is called an abortive depolarization in this report. The arrows in Fig. 3A show the typical abortive depolarization at 6 minutes after the administration of 10^{-5} of reserpine. The interval between the foregoing spike and the abortive depolarization was longer than that between the abortive depolarization and the succeeding spike. The abortive depolarization usually did not return to the original level of the maximal diastolic potential, so that the next prepotential started from the elevated level to fire the succeeding spike potential. In some cases of the abortive depolarization the next prepotential started without the manifestation of any repolarization sign. In the course of reserpine action the height of the abortive depolarization was markedly depressed and this depolarization finally disappeared.

Thus, there were two ways of the decrease of frequency in the pacemaker potential after reserpine. The first was that some of the usual spike potentials turned to the abortive depolarization which gradually increased in number. The other way was that the interval between each spike potential became longer, so that the decrease of the

frequency resulted. Usually the decrease of the frequency appeared in a mixed way of these two.

In some of the preparations there appeared many abortive depolarizations before the complete abolishment of the pacemaker potential, as shown in Fig. 8A.

Whenever the pacemaker spike had disappeared and the abortive depolarizations of the pacemaker

had appeared, the usual spike pattern of the non-pacemaker did not appear. The result is shown in Fig. 6B. On the other hand, the abrupt disappearance of the depressed pacemaker potential is illustrated without the manifestation of further fluctuating abortive depolarization in Fig. 3.

As mentioned above, when a considerable decrease of the frequency of the potential and an appearance of the abortive depolarization after reserpine were observed, the pacemaker spike was not much affected, and the atrial non-pacemaker potential was not evoked by the abortive depolarization of the pacemaker but was evoked by the pacemaker spike potential. On the other hand, when the notched potential changed to the *notch-potential* in response to reserpine, the frequency of the atrial non-pacemaker spike potential was the same as that of the *notch-potential* (Fig. 6A). Even in the case in which the *notch-potential* appeared by reserpine, the pacemaker and the atrial non-pacemaker potentials remained normal. This may give some clues on the mode of the notched potential.

3) Antagonistic effect of adrenaline on reserpine action

The *notch-potential* induced by the administration of 10^{-5} of reserpine was recovered to the original notched potential in response to adrenaline. The concentration of adrenaline to antagonize the reserpine action differed considerably in each preparation, but was usually in the range of concentration of 10^{-7} to 10^{-5} . At first the magnitude of the *notch-potential* gradually increased and one to two minutes after the administration of adrenaline there started the spike potentials at the peak of the *notch-potential* followed by the increase of the frequency. Several minutes were required to restore the normal notched potential. In this case some of the notchings seemed to be masked by the

FIG. 8. Comparison of the mode of disappearance of the pacemaker potential (A) with that of the *notch-potential* (B) in response to reserpine.

FIG. 9. Effects of 10^{-6} of adrenaline on the *notch-potential* induced by the administration of 10^{-5} of reserpine.

increased spike potential. Fig. 9 shows the antagonistic effects of 10^{-6} of adrenaline on the *notch-potential* caused by the administration of 10^{-5} of reserpine. As seen in the figure, though the threshold potential of prepotential remained unchanged, the increase of the slope of prepotential and the slight increase of the maximal diastolic potential were observed. These effects of adrenaline were opposite to the effects of reserpine.

The similar antagonistic effects of adrenaline were also observed on the depressed pacemaker potential induced by the administration of reserpine. One to three minutes after adrenaline the abortive depolarization suddenly appeared between the spikes and then some of the abortive depolarizations fired to the spikes, resulting in the increase of the frequency. At last the complete restoration of the spike potential and the increase of the frequency were obtained.

FIG. 10. Effects of 10^{-7} and 10^{-6} of adrenaline on the pacemaker potential affected by reserpine.

The result is shown in Fig. 10. The concentration of adrenaline to antagonize the reserpine action on pacemaker potential did not show any marked difference from that of the amine on the *notch-potential* induced by the same procedure, and was also subjected to a considerable individual variation.

4) *The irreversibility of the reserpine action by the replacement of the modified Tyrode solution*

When the full depression of the notched or pacemaker potential by reserpine had developed, the repeated replacement of the nutrient solution in which the preparation was immersed did not restore the normal pattern and the normal rhythm of the potentials. Sometimes the depression of the spike became more marked by this procedure. In these cases adrenaline also antagonized the reserpine effects. The antagonistic effects and concentration of adrenaline on either notched potential or pacemaker potential were almost the same irrespective of the presence of reserpine in the nutrient solution.

DISCUSSION

Some of the transmembrane potentials which were recorded from the vicinity of the sinoatrial node of rabbit's heart by use of the microelectrode technique differed from the pacemaker and the atrial non-pacemaker potentials. The characteristic figures of the potential consisted in the notching between the diastolic potential and the upstroke of the spike potential, and in the long duration of the depolarization phase. This potential coincided with the notched potential described by West, being taken from the triangular part of the sinoatrial node of rabbit. The similar notched potential recorded from the

atrioventricular node was suggested by Sono *et al.* (4) to play some important role in the conduction of impulse through the node. Hoffman *et al.* (3, 9) reported that the administration of acetylcholine to the atrioventricular node of the extirpated rabbit's heart revealed the notched potential followed by the retarded and markedly depressed depolarization. They discussed the possibility that the development of the notched potential resulted from the decremental conduction of impulse through the specialized structure of the atrioventricular node. They further suggested that the notched potential in the atrioventricular node might have some relation to the histological convergence of small muscle fibers to a large fiber. This convergence of the muscle fibers might cause a conduction delay and a decremental conduction of impulse.

In the present studies the response of the notched potential to reserpine and adrenaline was compared with those of the pacemaker and the atrial non-pacemaker potentials. The notched potential was much sensitive to reserpine. Although some decrease of the frequency of the potential occurred for all the potentials about 20 to 40 minutes after the administration of 10^{-5} of reserpine, the notched potential was depressed more markedly than the other potentials, and at last the spike of the notched potential disappeared before the development of the marked depression of the other potentials. There remained a small wave which was called as *notch-potential*. This *notch-potential* was very similar in shape to the slow potential described by Goto *et al.* (5, 10) in the uteri of rat and mouse. Using microelectrode technique they recorded the notched potential in response to electrical stimuli of a certain range of intensity. The duration and height of the notching also varied with the intensity of the stimuli. In response to subthreshold stimuli the uterus showed only the notching which did not fire to the spike. They discussed the possibility of the notching to result from the local electrotonic change of the muscle fiber from the adjacent stimulated fibers. The time course of the *notch-potential* in the present experiment was very close to that of the slow potential recorded by Goto *et al.*

Marshall (8) also recorded a small potential, like the so-called *notch-potential* in this paper, from the sinoauricular preparation of rabbit's heart which was cooled about 11°C *in vitro*. Besides, the pacemaker potential of the cooled preparations was some what depressed, while the atrial non-pacemaker potential did not fire to a usual spike potential. She suggested that the dissociation of both potentials in response to the cooling resulted from the decrease of the diastolic potential of the pacemaker and the non-pacemaker, and interpreted that the administration of acetylcholine elicited propagated action potential in the non-pacemaker because of an increase in the diastolic membrane potential toward the normal level. In the present experiment, however, neither the decrease of diastolic potential in the non-pacemaker nor the conduction blockade from pacemaker to atrial non-pacemaker was observed throughout the reserpine action. The maximal diastolic level of pacemaker potential was slightly decreased without any change in the threshold potential after reserpine.

The notched potential usually had a prepotential and a notching followed by the spike potential. There are two possibilities to elucidate the mechanism of the prepoten-

tial in the notched potential. The first is an electrotonic response of the muscle fiber propagated from the pacemaker fiber which has an automatic rhythm. But this may be less possible because of a slow onset and long duration of the prepotential. Another possibility is that the muscle fiber from which the potential was recorded might have an automaticity independent on the pacemaker activity. But there is no evidence to support this mechanism.

Three possibilities on the genesis of the notching may be suggested. The first possibility is that an electrotonic response might be conducted to the muscle fiber in the notched area through a narrow bridge which lies between muscle fibers of the sinoatrial node and is enough small in safety factor for the conduction of impulse. There is also another mechanism which interferes the conduction of impulse. Hoffman *et al.* (3) also suggested that the intercalated discs which transversely cross the muscle fiber of the heart might interfere the conduction. The second possibility is the suggestion of the existence of different pathways for the conduction of impulse from the pacemaker to the muscle fiber in the notched area. As shown in Fig. 7D and 7E, the fact that the notched potential was separated into two components, a *notch-potential* and a notched potential, in response to reserpine may result from the delayed arrival of the impulses from the pacemaker and consequently from time difference of arrival to the muscle fiber via a collateral pathway. In other words, the effect of reserpine on the notched potential is interpreted that the full spike was not fired in response to the first stimulus, and that the other delayed impulse from the pacemaker arrived at the muscle fiber and elicited firing. The third possibility is that the notching might be a junction potential transmitted across the muscle junction which was suggested to be a discontinuous space between muscle fibers (Goto *et al.*) within the sinoatrial node. However, there may be no evidence to doubt the syncytial structure of the heart muscle.

In the course of reserpine action the *notch-potential* was markedly depressed. The administration of adrenaline increased the height of the depressed *notch-potential*. When the height of the *notch-potential* reached a critical level, the notching fired to a usual notched potential. Accordingly, the height of notching seemed to be a determining factor for the firing of the notched potential. As seen in Table 2, the level of flexion from prepotential to notching was frequently stable at a definite period of reserpine action, while the level of flexion from notching to the upstroke of the spike gradually rose during the same period. If the latter level of flexion is a determining factor for firing of the notched potential, it gradually rises in the course of reserpine action. At the same time, the level of threshold in the pacemaker remained unchanged during the reserpine action.

In some of the records from pacemaker area the abortive depolarization appeared in the course of reserpine action before the abolishment of the pacemaker potential. The similar pattern has already been shown by West *et al.* (11). They reported that when adrenaline was administered to the preparation, the abortive diastolic prepotential appeared between the normal pacemaker potentials and reached threshold to fire. Such

firing of the abortive diastolic prepotential by adrenaline resulted in the increase of rate of the potential. The similar result was obtained in the present experiment. The height and frequency of the abortive depolarization in the preparation treated by reserpine gradually increased after the administration of adrenaline and at last reached threshold and fired. The antagonistic effect of adrenaline on the *notch-potential* was almost the same as that of adrenaline on the abortive depolarization.

The effects of reserpine on the pacemaker potential of the extirpated rabbit's heart were studied in the previous report (1). The administration of 10^{-6} of reserpine depressed the spike potential and the frequency of the pacemaker, and at last abolished them. The similar effects of reserpine on the notched potential of the same preparation were also obtained in this experiment, though the effects of reserpine appeared much faster on the notched potential. These results seemed to have some relation with the depletion of catecholamines from the heart by reserpine. The depletion of catecholamines from the heart by reserpine was already shown by many authors. The catecholamines of the rabbit's heart consist in largely *noradrenaline* [98% by Muscholl (12), 97% by Paasonen *et al.* (13)]. Matsuo in this laboratory studied the effects of reserpine on the *noradrenaline* content of rabbit's heart *in vitro* and *in vivo* (personal communication). When 1.0 mg/kg of reserpine was injected intravenously 16 to 20 hours before the experiment, the decrease of *noradrenaline* was more than 90%. The extirpated heart of this animal pretreated with reserpine showed almost normal configuration of the potential, though the potential showed a decreased rhythm. On the other hand, 2 or 3 hours after the administration of 10^{-5} of reserpine all the pacemaker, the notched and the non-pacemaker potentials of the extirpated heart were abolished and then the decrease of *noradrenaline* was only 30 to 40%. The discrepancy of the depletion of *noradrenaline* by reserpine *in vitro* and *in vivo*, and the discrepancy of the response of the potential to depletion of *noradrenaline* from the heart muscle by reserpine need some interpretation. Schümann *et al.* (14) already postulated that the denervation of adrenal gland in rabbit decreased the amount of depletion of catecholamines by reserpine. As was shown in the previous experiment, the restarting concentration of adrenaline on the stillstanding potential which had lost its normal rhythm by reserpine did not differ markedly irrespective of the washing-out of reserpine from the preparation. Moreover, Tachi and Matsuo (personal communication) showed that the content of *noradrenaline* of the restarted heart by adrenaline was almost the same as that of the stillstanding heart by reserpine, the amines of both preparations being reduced by about 30% of the normal content. Their results show that the minute amount of amines which was not detected by the chemical assay of catecholamines employed, restarted the stillstanding heart by reserpine. It is assumed that though the heart of the animal which was injected with 1.0 mg/kg of reserpine intravenously, was depleted about 90% of the content of *noradrenaline*, the potential pattern of the heart was maintained by the minute amount of the endogenously liberated amines. On the contrary, the extirpated heart which was treated by reserpine and was deprived of 30% of *noradrenaline* could not liberate enough endogenous catecholamine to maintain

its normal pattern of the potential.

Bülbring and Burn (15) suggested that the endogenously liberated acetylcholine from the heart muscle fiber initiated and maintained the rhythmic contraction of the heart. The results in the present experiment also show that the minute amount of catecholamines endogenously liberated from the sinoatrial node plays the similar role in initiation and maintenance of the pacemaker and the notched potentials. The responses of the notched potential to reserpine and adrenaline may give some contribution to elucidate the mechanism of the pacemaker activity.

SUMMARY

By use of microelectrode technique the notched potential is recorded from the vicinity of the pacemaker area of the extirpated rabbit's heart. The notched potential is characteristic in a notching before the manifestation of the upstroke of the action potential, and in a slow rise of the depolarization. This potential also responds somewhat differently to reserpine and adrenaline from the pacemaker and the atrial non-pacemaker potentials.

Before the manifestation of the marked depression of the pacemaker and the atrial non-pacemaker potentials by a dose of 10^{-5} of reserpine, the notched potential changes to the *notch-potential*, which is a small electrical pattern (about 6 to 20 mV in height) without a spike. Furthermore, the *notch-potential* gradually decreases in height and at last disappears with the abolishment of the pacemaker potential.

In response to adrenaline the *notch-potential* increases in height. When the magnitude of the potential becomes high enough to fire, the spike potential follows. On the other hand, the depressed pacemaker potential by reserpine increases in height and frequency after the administration of adrenaline until the full pacemaker potential appears. The abortive depolarization, which sometimes appears between the depressed pacemaker spikes in the course of reserpine action, is a small pattern of electrical wave. Further, the abortive depolarization caused by reserpine fires to the normal spike in response to a definite concentration of adrenaline.

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