EFFECTS OF ANGIOTENSIN II AND 1-SAR., 8-ISOLEU. ANGIOTENSIN II ON ELECTRICAL AND MECHANICAL PROPERTIES OF THE PORTAL VEIN FROM RATS OF DIFFERENT AGES

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Accepted April 11, 1979

Abstract—The effects of angiotensin II (Ag-11) and 1-sar., 8-isoleu. angiotensin 11 (anti-Ag-11) on the membrane and mechanical properties of smooth muscle cells of the rat portal vein were investigated in three different age groups (6–8 weeks, immature rat; 3–5 months old, young rat and 13–15 months old, adult rat). Application of Ag-11 (10^{-10} \text{g/ml}) did not depolarize the membrane, but did increase the spike frequency and potentiated the frequency and amplitude of twitch contraction. In a concentration of more than 10^{-9} \text{g/ml} Ag-II, the membrane was depolarized and a phasic contracture was developed in three age groups. Depolarization of the membrane produced by Ag-II could be classified into two components, i.e. phasic and tonic depolarizations. In adult rats, Ag-II produced the highest amplitude of the depolarization in three age groups but tonic depolarization showed nearly the same amplitude as that observed in immature rats. These phenomena indicate that the sensitivity of smooth muscle cell membrane to Ag-II increases with age up to 3–5 months and that an increased sensitivity is accompanied by a generation of desensitization. Tachyphylaxis to Ag-II was also observed by repetitive applications, but the appearance depended on the stimulus conditions. Anti-Ag-II, itself slightly increased the spike frequency and the amplitude of twitch contraction. However, under pretreatment with anti-Ag-II (10^{-9} or 10^{-7} \text{g/ml}), the actions of Ag-II on the electrical and mechanical activities were markedly suppressed in the three age groups. When the dose-response curve was obtained from the mechanical response produced by Ag-II, the relation shifted to the right in the presence of anti-Ag-II in all age groups. In the presence of 10^{-7} \text{g/ml} anti-Ag-II, no contracture was evoked by application of 10^{-6} \text{g/ml} Ag-II in three age groups. Anti-Ag-II seems to possess a higher affinity to the angiotensin receptor than does Ag-II.

Excitatory actions of angiotensin II (Ag-11) on the mechanical or electrical activity of various visceral smooth muscles have been investigated [taenia coli of the guinea-pig (1, 2), mesenteric veins of the rabbit and dog (3), and the rat myometrium (4, 5)], and this agent consistently depolarized the membrane and increased the spike frequency. Carruba et al. (4) studied the Ag-11 action on the contraction of isolated rabbit, guinea-pig and rat portal veins, and concluded that Ag-11 proved to be the most active drug on the rat portal vein but exhibited only a slight increase in mechanical activity of the guinea-pig and rabbit preparations. Weston and Golenhofen (6) also reported that Ag-11 produces an excitatory action on the rat and rabbit portal veins but that it showed an inhibitory action on the guinea-pig portal vein. These results suggest the species differences of Ag-11 actions. It
is also known that most smooth muscle tissues reduce the response to Ag-11 following repeated exposure to Ag-11, i.e. appearance of tachyphylaxis. However, tissues such as the cat papillary muscle (7), rabbit aorta (8, 9), rat stomach muscle (8), rabbit coeliac artery (10) and rabbit and rat portal veins (6) do not develop tachyphylaxis to Ag-11.

Recently, the maturation of vascular reactivity of Ag-11 in neonatal lambs during the immediate postnatal period has been investigated and it was concluded that the response of the vascular tissue to Ag-11 is dependent on aging (11). From similar lines of experiment done on the different species, much the same conclusions were reached (12, 13, 14). For example, Kuriyama and Suzuki (14) reported that sensitivity of the muscle cell of the superior mesenteric artery of the rabbit to acetylcholine was drastically changed during the progress of aging.

As the effects of Ag-11 and its derivative on the membrane activity have apparently been systematically investigated, we investigated the effect of Ag-11 and anti-Ag-11 on the electrical and mechanical properties of the rat portal vein. The second aim was to observe the effects of Ag-11 on smooth muscle cells of the rat portal vein in different ages.

MATERIALS AND METHODS

We used Wister strain rats and classified them into three age groups, immature (6–8 weeks), young (3–5 months) and adult (13–15 months). The rats were stunned and bled, the portal vein was excised and the connective tissue was carefully removed in Krebs solution at room temperature under a binocular microscope.

Strips of portal vein of 10–15 mm in length and 1–1.5 mm in width were cut along the longitudinal axis. The tissue was mounted in an organ bath 2 ml in capacity, through which solution flowed continuously at a temperature of 35–36°C. The solution was perfused at a rate of 3 ml/min. The microelectrode was inserted into the muscle cell from the outer surface of the portal vein. The intracellular recordings were made with glass capillary microelectrodes filled with 3 M KCl. Measurement of the membrane activity was made after 60–90 min perfusion in the organ bath (15). To record the mechanical activity, the portal vein of 10–15 mm in length and 1–1.5 mm in width was cut along the longitudinal axis. Two pieces of the tissues were mounted in parallel in the same organ bath which had a vertical tubular shape and a volume of 2 ml. One end of the tissue was fixed at the bottom of the bath and the other end was connected to an isometric tension recorder by a thread. The solution was perfused at a rate of 3 ml/min.

Modified Krebs solution which had the following ionic composition (mM) was used; Na⁺, 137.4; K⁺, 5.9; Mg²⁺, 1.2; Ca²⁺, 2.5; HCO₃⁻, 15.5; H₂PO₄⁻, 1.2; Cl⁻, 134.0 and glucose, 11.5. The solution was aerated with 97% O₂ and 3% CO₂, and pH was adjusted to 7.2.

Drugs used in the present experiments were angiotensin II (CIBA) and 1-sar., 8-isoleu. angiotensin II (Daiichi), tetrodotoxin (Sankyo) and phentolamine (CIBA-Geigy). Ag-II and anti-Ag-II were kept in a freezer (–20°C) and were dissolved with Krebs solution just before the experiment. The final concentrations of the drugs were expressed as g/ml.
RESULTS

Effects of Ag-II and anti-Ag-II on the membrane potential: The membrane of smooth muscle cells of the portal vein of young rat was spontaneously active, and a burst discharge appeared between the silent periods. The mean membrane potential measured at the maximum value during the silent period between spike generations was $-48.4 \pm 3.5$ mV, S.D. ($n=84$), and this value was the same as that observed from immature and adult ones ($-47.9 \pm 3.0$ mV, $n=77$; $-48.8 \pm 2.5$ mV, $n=52$, respectively). These membrane potential values were the same as those observed in tissues from the guinea-pig (16, 17). Changes in the membrane potential of smooth muscle cells were measured before and during application of Ag-II and also in the presence or absence of anti-Ag-II. The microelectrode was repetitively inserted into the cells and the value was only cited when the recorded membrane potential was within the range of real-time observations.

![FIG. 1. Effects of angiotensin-II and I-sar., 8-isoleu. angiotensin II (anti-Angio) on the membrane potential of the portal vein of a young rat. Angiotensin II ($10^{-10}$, $10^{-6}$ g/ml) and anti-Angio. ($10^{-9}$ and $10^{-7}$ g/ml) were used. Dotted lines in the figure indicate the mean membrane potential measured before application of the agents ($2 \times$ S.E. $n=15-30$). After application of the agent, membrane potentials were recorded by successive insertions of the microelectrode.](image-url)
potential stayed at the same level more than 5 sec. Before application of Ag-II, the mean membrane potential with S.E. (n=15–30) was recorded and this value was registered as the control value.

Figure 1 shows the effects of Ag-II on smooth muscles of the portal vein of young rats. Application of Ag-II (more than $10^{-9}$ g/ml) produced depolarization of the membrane lasting 5–10 min (phasic depolarization) and then the membrane was slightly or markedly

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**FIG. 2.** Effects of Agiotensin II ($10^{-10}$–$10^{-6}$ g/ml) and anti-Angio. ($10^{-9}$–$10^{-7}$ g/ml) on the membrane potential of the portal vein of an immature rat. Experimental procedures and measurements of the membrane potential were the same as those described in Fig. 1.

**FIG. 3.** Effects of Angiotensin II ($10^{-10}$–$10^{-6}$ g/ml) and anti-Angio. ($10^{-9}$ g/ml and $10^{-7}$ g/ml) on the membrane potential of the portal vein of adult rat. Experimental procedures and measurements of the membrane potential were the same as those described in Fig. 1.
repolarized to a certain level above the control value (tonic depolarization). Increased concentration of Ag-II (10^{-7} or 10^{-6} g/ml) enlarged the amplitudes of phasic and tonic depolarizations. By application of anti-Ag-II (10^{-10} to 10^{-6} g/ml) the membrane potential was not changed. However, following pretreatment with anti-Ag-II (10^{-9} or 10^{-7} g/ml), the effects of Ag-II on the membrane potential were markedly suppressed, and in the presence of 10^{-7} g/ml anti-Ag-II no depolarization was observed by treatment with 10^{-6} g/ml Ag-II.

Similar experiments were carried out on immature and adult rats. Figs. 2 and 3 show the effects of Ag-II (10^{-10}–10^{-6} g/ml) and anti-Ag-II (10^{-9} and 10^{-7} g/ml) on the membrane potential recorded from immature (Fig. 2) and adult rats (Fig. 3). When depolarizations induced by Ag-II (10^{-6} g/ml) were compared between two different age groups, phasic depolarization was larger in adult rats than that in immature ones (the mean depolarizations were 18 mV, n=3 and 10 mV, n=3, respectively). In adult rats, the phasic depolarization rapidly declined to the level close to the control value. On the other hand, in immature rats, the phasic depolarization gradually declined, and therefore, difference between phasic and tonic depolarizations was not significant (6 mV, n=3 in adult rats, and 7 mV, n=3 in immature ones). The mean amplitudes of phasic and tonic depolarizations produced by Ag-II in young rats were much the same as those observed in adult rats (16 mV and 6 mV, respectively, n=3).

Figure 4 shows the effects of various concentrations of Ag-II on the membrane potential of portal vein of young rats measured at a steady level during application of Ag-II in the presence (10^{-9} or 10^{-7} g/ml) or absence of anti-Ag-II. The membrane was depolarized by treatment with 10^{-9} g/ml Ag-II from −47.2±1.1 mV, S.D. (n=43) to −45.1±2.3 mV, S.D. (n=17, p<0.05), and increased concentration of Ag-II further depolarized the membrane (from −47.2±1.1 mV to −41.3±1.8 mV, S.D. n=18, by 10^{-7} g/ml). Under pretreatment with 10^{-9} g/ml anti-Ag-II, the membrane was only depolarized by application of 10^{-6} g/ml Ag-II (from −49.3±1.9 mV, S.D. n=45 to −44.1±2.6 mV, S.D. n=15, p<0.05). However, by pretreatment with 10^{-7} g/ml anti-Ag-II, depolarization was not observed (from

![Fig. 4. Relationships between the membrane potentials and concentrations of angiotensin II (10^{-10}–10^{-6} g/ml) in the presence or absence of anti-angiotensin II (10^{-9} or 10^{-7} g/ml). The tissues were excised from the portal vein of the young rats. ×; Angiotensin-II alone. ○; Angiotensin-II with 10^{-9} g/ml anti-angiotensin-II. ●; Angiotensin-II with 10^{-7} g/ml anti-angiotensin-II. Horizontal bars indicate 2 × S.D.](image-url)
These effects of anti-Ag-II on the Ag-II induced depolarization were also observed in immature and adult rats.

The effects of Ag-II (10^{-10}–10^{-6} g/ml) on the membrane potential and electrical activity were not modified by treatment with tetrodotoxin (10^{-7} g/ml) or phentolamine (10^{-7} g/ml). These effects of Ag-II and anti-Ag-II on the membrane potentials recorded from three different age groups indicate that sensitivity of the smooth muscle cell membrane to Ag-II is gradually increased with aging, and increased sensitivity to Ag-II accompanies desensitization. Marked differences were observed between immature and adult rats, but the findings in young rats were closer to those in the adults rather than the immature rats. The inhibitory action of anti-Ag-II on the Ag-II action was consistently observed in the three age groups.

Effects of Ag-II and anti-Ag-II on the membrane activity: Figure 5 shows the various patterns of spontaneous discharges recorded in Krebs solution. When the membrane potential was low (a, b and e), higher spike frequency with lower spike amplitude was observed. The reversed sequences were observed at the high membrane potential (c, d and h). Variations of the electrical activity may to some extent be due to differences of the experimental conditions, namely grade of stretch of the tissue, time after excise of the tissue or temperature of the organ bath. These various patterns of the electrical activity were consistently observed in tissues from immature (a and b), young (c, d and e) and adult rats (f, g and h) and these was no apparent difference among the three age groups. The effects of Ag-II (from 10^{-10} to 10^{-6} g/ml) and anti-Ag-II (10^{-9} and 10^{-7} g/ml) on the membrane activity were observed.

Figure 6 shows the effects of Ag-II and anti-Ag-II on the membrane activity of smooth muscle cells of the portal vein of young rats. Application of 10^{-9} g/ml Ag-II slightly depolarized the membrane and increased the spike frequency (a). However, 10^{-9} g/ml Ag-II

![Figure 5](image-url)
neither depolarized nor increased the spike frequency under pretreatment with 10^{-9} g/ml anti-Ag-II (b). Application of 10^{-8} g/ml Ag-II markedly depolarized the membrane and produced a depolarization block of the spike generation (c). These excitatory actions produced by 10^{-8} g/ml Ag-II were markedly suppressed by pretreatment with 10^{-9} g/ml anti-Ag-II but the spike frequency remained (d). Following pretreatment with 10^{-9} g/ml anti-Ag-II, 10^{-8} g/ml Ag-II depolarized the membrane and increased the spike frequency but excitatory actions were markedly suppressed (e). Anti-Ag-II (10^{-8} g/ml) slightly increased the spike frequency without any depolarization of the membrane (f). These changes of electrical activities produced by Ag-II and with anti-Ag-II were also recorded from immature and adult rats.

Figure 7 shows the effects of prolonged application of Ag-II (10^{-8} g/ml) on the membrane activity observed from the young rat. In the presence of Ag-II, the amplitude of phasic depolarization was gradually reduced to a certain repolarized level after 7 min (b). After 13 min, burst discharges reappeared between the silent periods, the spike frequency was still higher and the duration of burst discharge was longer than that of the control (d). These changes of the electrical activity observed in the presence of Ag-II strongly indicated the appearance of desensitization. All the electrical activities illustrated in Fig. 7 were recorded from the same preparation and the records from (b) to (d) were obtained successively from

![Fig. 6. Effects of angiotensin II and anti-angiotensin II on the membrane activity of smooth muscle cells of the portal vein of young rat. b, d and e; before application of Ag-II, anti-Ag-II was pretreated. f; application of anti-Ag-II (10^{-8} g/ml). Horizontal bar under the record indicates the period of application of Ag-II, except in f.](image-url)
the same cell. The suppression of electrical activities and repolarization of the membrane under prolonged treatment with Ag-II were not due to inactivation of Ag-II itself, because with reapplication of this solution to fresh tissue, the membrane showed nearly the same response as was observed in the previous experiment.

Effects of Ag-II and anti-Ag-II on the mechanical activity: Figure 8 shows the effects of Ag-II and anti-Ag-II on the spontaneously generated twitch contraction recorded from smooth muscles of the portal vein of young rats. By application of $10^{-10}$ g/ml Ag-II, the frequency of twitch contraction and the amplitude of contraction were slightly increased. In a concentration of more than $10^{-9}$ g/ml, Ag-II elevated the resting tension level as phasic and tonic contractures. Generation of phasic contracture produced by Ag-II might be related to the development of phasic depolarization. When the amplitude of tonic depolarization was low, the tonic contracture did not occur yet the frequency and amplitude of twitch tensions increased. Application of anti-Ag-II ($10^{-8}$ g/ml) slightly increased the frequency of twitch contraction in all age groups. These actions of anti-Ag-II on the mechanical response evoked from three age groups were the same as those observed from the change in the membrane activity.

In the presence of anti-Ag-II, the effects of Ag-II on the mechanical activity were markedly suppressed, i.e. by application of $10^{-8}$ g/ml anti-Ag-II, the frequency of the twitch contraction and the amplitude of phasic contracture produced by $10^{-8}$ g/ml Ag-II were markedly suppressed. In the presence of $10^{-7}$ g/ml anti-Ag-II, the frequency of twitch contraction was slightly increased but phasic contracture was not generated by application of $10^{-6}$ g/ml Ag-II in all age groups. These changes of the mechanical activity induced by Ag-II in the presence or absence of anti-Ag-II were much the same as those observed from
the membrane activity. Therefore, the effects of Ag-II and anti-Ag-II on the mechanical property can be assumed from the changes in the membrane activity.

Figure 9 shows the relationship between amplitudes of phasic contracture and concentrations of Ag-II in immature, young and adult rats. Increased concentration of Ag-II increased the amplitude of phasic contracture. The absolute amplitude of phasic contracture was consistently larger in adult rats than that in immature ones. However, when the amplitude of contracture evoked by application of 10^{-6} g/ml Ag-II was registered as 100\% in each age group, the relative amplitude of phasic contracture evoked by 10^{-9}-10^{-6} g/ml Ag-II in young rats was consistently larger than that observed in the other age groups, i.e.
in young rats, application of 10^-8 g/ml Ag-II produced nearly the same amplitude of phasic contracture as that observed by treatment with 10^-1 g/ml Ag-II.

When the dose-response relations were compared in three age groups in the presence or absence of anti-Ag-II (10^-9 g/ml or 10^-1 g/ml), these relations shifted to right in the presence of 10^-5 g/ml anti-Ag-II and the amplitude of phasic contracture produced by 10^-6 g/ml Ag-II never reached the maximum value (100%) in any group. Moreover, following pretreatment with 10^-7 g/ml anti-Ag-II, 10^-6 g/ml Ag-II never evoked the phasic contracture in all three age groups. These results suggested that anti-Ag-II suppressed the generation of phasic contracture produced by Ag-II but not in the manner of a competitive antagonist.

When 10^-6 g/ml Ag-II was applied to the tissue repetitively, the amplitudes of mechanical response of the muscle were reduced, but such were dependent on the experimental conditions. For example, by application of 10^-6 g/ml Ag-II for 3 min duration at 15 min intervals, amplitudes of phasic contraction were the same as those observed from the initial response, but when Ag-II was applied for 5 min duration at 15 min intervals, the responses were gradually lowered to a certain level. This means that the appearance of tachyphylaxis depended on the stimulus condition.

**DISCUSSION**

In all three age groups, Ag-II depolarized the membrane and increased the spike frequency. The minimum concentration of Ag-II which led to an increase in the spike frequency

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**Fig. 9.** Dose-response relationships obtained from smooth muscle tissues of the rat portal vein. Three different age groups used were: immature (○; 6-8 weeks), young (×; 3-5 months) and adult (●; 13-15 months). Concentrations of Ag-II were expressed on log scale, and the maximum tension recorded by application of 10^-6 g/ml Ag-II was registered as 100%. These relationships were also observed under pretreatment with 10^-9 or 10^-7 g/ml anti-Ag-II.
was $10^{-10}$ g/ml. These excitatory actions of Ag-II on the muscle cell were attributed to direct actions on the muscle cell as the $\alpha$-adrenergic blocking agent, phentolamine and the nerve blocking agent, tetrodotoxin, had no effect on the Ag-II actions on the membrane and mechanical activities. Depolarization of the membrane produced by prolonged treatment with Ag-II was classified into two components, i.e. phasic and sustained tonic depolarizations. The former probably produces a phasic contracture of smooth muscle cell while the latter mainly enhances the amplitude and frequency of twitch contraction. The amplitudes of phasic depolarization and contracture depended on the concentration of Ag-II and the age of the rat from which the tissue had been obtained.

Smooth muscles of the portal vein excised from adult rats showed higher phasic depolarization in response to Ag-II than that observed from immature rats. However, the difference in response to Ag-II between young and adult rats was not significant. These results indicate that the sensitivity of smooth muscle tissues to Ag-II may develop in parallel with the progress of aging, up to 3-5 months (young rats). Similar conclusions were reached by other investigators on the neonatal lamb carotid arteries and the portal veins from newborn rats, rabbits and guinea-pig (11, 12). However, this conclusion concerning the relationship between drug sensitivity and aging may not be generalized, because in the rabbit mesenteric artery the sensitivity of smooth muscle membranes to acetylcholine (hyperpolarizing action) declined gradually with aging (14). Some investigators (3, 6, 18) ruled out the generation of tachyphylaxis of excitatory response to Ag-II in the portal vein. On the other hand, Shepherd and Van Houtte (19) reported a controversial conclusion that tachyphylaxis appeared on the rat portal vein by treatment with Ag-II. These discrepancies might be due to differences in the experimental design, namely concentration of the agent, duration of application and interval between drug applications. From the present experiments, therefore, it is concluded that the appearance of tachyphylaxis is presumably a general feature of this tissue.

It is known that an analog of Ag-II, 1-sar., 8-isoleu. Ag-II (anti-Ag-II), has a potent and long-lasting competitive antagonistic effect against Ag-II when tested for its myotropic action on the isolated rabbit aorta, for its effect on blood pressure in anesthetized cats and dogs (5), and also for motility of excised rat stomach and rat uterus (20). Hall et al. (20) also postulated that sarcosine in position 1 protects the peptide against enzymatic degradation and enhances its half-life. Furthermore the modification in both positions 1 and 8 are important for the in vivo antagonistic potencies of Ag-II analogs. The electrical and mechanical activities observed in the present experiments showed that, 1-sar., 8-isoleu. Ag-II ($10^{-9}$ and $10^{-7}$ g/ml) slightly increased the spike frequency without depolarization, but they suppressed the depolarization and electrical activity induced by Ag-II in all three age groups. These results confirmed the previous observations made on the mechanical activity (5, 20) and indicate that anti-Ag-II possesses a stronger affinity to angiotensin receptor than does Ag-II.

Prolonged application of Ag-II produced a desensitization of the membrane and a large depolarization was accompanied by a large desensitization. Even when anti-Ag-II ($10^{-7}$ g/
ml) was continuously applied more than 30 min before application of Ag-II, the inhibitory effect of anti-Ag-II on the Ag-II action was not modified (Y. Takata, unpublished observations). This means that anti-Ag-II does not produce desensitization of the receptor.

Further investigations are under way to clarify whether or not desensitization produced by prolonged application of Ag-II is solely due to the inhibition of the receptor action.

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