Effects of Adrenaline and Noradrenaline upon the Microvibration on the Body Surface

Katsuzo FUZIWARA

The First Department of Physiology, Faculty of Medicine, Hirosaki University, Hirosaki, Japan.

Received for Publication September 1, 1966

The effects of adrenaline and noradrenaline upon the microvibration (MV), led from the body surface over the thigh muscles of the rabbit were observed. The MV, led with a Rochelle salt pick-up (Nihon Kohden Co.), was amplified and traced by an amplifier and ink-writing oscillograph simultaneously with the recording of the electroencephalogram (EEG), electrocardiogram (EKG), heartbeat, and sometimes respiratory movements. Unanesthetized animals were used, and adrenaline and noradrenaline were given intravenously. With an injection of smaller amounts of adrenaline or noradrenaline, there were observed facilitatory changes in the amplitude and frequency of the MV. And the facilitatory effects were observed to be suppressed by benzylimidazoline in an adequate dose. With an injection of larger amounts, on the other hand, the inhibitory effects of adrenaline and noradrenaline were recognized to be caused following transiently facilitatory changes in the MV and EEG. Such facilitatory and inhibitory effects of adrenaline were found to be considerably stronger than those of noradrenaline. The inhibitory effects of adrenaline and noradrenaline were inhibited completely or partially by sectioning the bilateral vagus nerves or administering an adequate dose of atropine. In most cases, there were concurrently seen the facilitatory and inhibitory changes on the heartbeat and EKG. From the above-mentioned results, it seems likely that the sympathomimetic drugs, such as adrenaline and noradrenaline, exert a facilitatory effect exclusively upon the MV led from the body surface over the skeletal muscles of the rabbit, and the inhibitory effect of adrenaline and noradrenaline, obtained by injecting larger doses, might be caused by the cardioinhibitory reflexes, because of its disappearance or decrease caused by the sectioning of the bilateral vagus nerves or the administration of atropine.

It has been described by ROHRACHER and YAMAUCHI, KAMACHI and INANAGA that there is a close relationship between the autonomic nervous system and the so-called microvibration (MV) on the body.
surface of human beings and animals, which can not be observed by visual inspection. Rohracher\textsuperscript{7,8,9,10} postulated that the generating mechanism of the MV may be related to the thermoregulatory autonomic nervous system, because the MV can not be seen in cold-blooded animals, but only in warm-blooded ones. It was, furthermore, shown by him\textsuperscript{8} that in a cold environment the MV increased in frequency and decreased in amplitude, while in a warm one it decreased in frequency and returned to the normal amplitude. Yamachi et al\textsuperscript{13} have, on the other hand, reported that there are seasonal changes in the frequency of the MV, which are deduced to be due to the seasonal variations in the autonomic nervous system. These results suggest that there are some relations between the MV and autonomic nervous system. However, so far as the action of sympathomimetic and parasympathomimetic drugs on the MV are concerned, there have been only a few investigations,\textsuperscript{3,4,11} and there is no consistent opinion yet. In the investigation of Inanaga\textsuperscript{3} and Sugano anb Inanaga\textsuperscript{11}, it was shown that there was no significant change in amplitude and frequency of the MV with the intravenous injection of autonomic nervous drugs, such as adrenaline, acetylcholine, atropine, pilocarpine, eserine, ergotamine and benzylimidazoline. On the other hand, Inoue\textsuperscript{4} reported that there was obtained either no change or a somewhat increased change in amplitude of the MV by an intravenous injection of adrenaline, while slightly decreased change of the MV by an injection of acetylcholine. Accordingly, the present experiments were attempted to clarify the action of the sympathomimetic drugs, such as adrenaline and noradrenaline, on the MV led from the body surface over the skeletal muscles of the rabbit.

METHODS

The experiments were performed on 40 male and female adult rabbits, weighing about 3 to 4 kg, unanesthetized. The rabbits were restrained with a fixing apparatus in a supine position in a dark and electromagnetically shielded room. No Flaxedil or d-tubocurarine were used. The MV which cannot be seen by visual inspection, was led with a Rochelle salt pick-up (Nihon Kohden Co. Tokyo) from the depilated lateral surface of the thigh in each experimental animal. In order to transform the mechanical vibration to an electrical one, the pick-up was attached to the body surface over the thigh muscles of the animal, exerting slight pressure so as to assure perfect contact between the skin and the entire face of the pick-up. The MV, transformed to an electrical vibration by this pick-up, was amplified and recorded by an amplifier and ink-writing oscillograph, respectively. The frequency characteristic of the pick-up used was approximately linear from 3 to 100 c/sec,
In addition to the MV, there were also recorded polygraphically the electroencephalogram (EEG) from the occipito-parietal regions and the electrocardiogram (EKG) or heartbeat, which was captured over the apex by the same pick-up as that in the MV. Respiratory movements were sometimes led off by attaching a respiratory pick-up of the thermister type to the nasal cavity as well. The time constant of the recording system was 0.3 for the MV, EEG and heartbeat, and 1.5 seconds for the EKG and respiratory movement records, respectively. L-adrenaline and DL-noradrenaline chloride (Sankyo Co.), diluted in 0.9 % saline solution, were injected intravenously into the ear vein in various doses. The duration of intravenous injection of adrenaline or noradrenaline was about a second per 0.1 cc in all cases. The experiments were performed at a room temperature of about 20 to 28°C, because the coldness often provoked a major tremor which disturbed the recording of the MV. The room was kept quiet so as not to give an acoustic stimulation to the experimental animals.

RESULTS

1. Action of adrenaline and noradrenaline on the MV in awaked resting rabbits.

In Figures 1 and 2 are illustrated the EEG, MV, heartbeat and EKG tracings recorded before and after the administration of adrenaline and noradrenaline.

Fig. 1. EEG (1. occipito-parietal lead), MV (r. thigh muscles), HB (heartbeat) and EKG (lead II) tracings before and after an injection of adrenaline in a dose of 1 μg per kg. A: Control EEG, MV, HB and EKG tracings before adrenaline injection. B and C: EEG, MV, HB and EKG tracings about 20 and 50 seconds after adrenaline injection, respectively. Each calibration in right side indicates 50 μV for the EEG and 1 mV for the MV, HB and EKG, respectively. Time in 1 sec. Note augmentative changes in amplitude and frequency of the MV.
noradrenaline in smaller doses, respectively. In the control tracing before an injection of adrenaline or noradrenaline, there could not be recognized the correspondence between the dominant vibration of the MV and the first vibration of the heartbeat or R wave of the EKG, which was described to be observed clearly in humans. With an intravenous injection of adrenaline or noradrenaline in a dose of 1 μg per kg of body weight, the MV was observed to augment considerably in the amplitude and frequency of vibration, as shown in Figure 1 and 2. This was also followed by facilitatory changes in the EEG and heartbeat, such as low amplitude fast activity and an increase in the amplitude of vibration, respectively. The shortening in heart rate could not be recognized, as shown in the R-R intervals of the EKG. The augmentative effect of adrenaline was shown to be considerably larger than that of noradrenaline, as illustrated in Figure 1 and 2.

In Figures 3 and 4 are shown the EEG, MV, heartbeat and EKG tracings recorded before and after the administration of adrenaline and noradrenaline in a moderate dose, respectively. When a moderate dose of adrenaline (10 μg per kg) was injected intravenously, it was observed to cause a marked and prolonged decrease following an immediate but transient increase in the amplitude and frequency of the MV. The injection of the same dose of noradrenaline as that of adrenaline, however, provoked facilitatory changes in the EEG, MV and heartbeat, without causing inhibitory ones.

In Figure 5 are represented the EEG, MV, heartbeat and EKG tracings recorded before and after an injection of noradrenaline in a
Fig. 3. EEG (1. occipito-parietal lead), MV (r. thigh muscles), HB (Heartbeat) and EKG (lead II) tracings before and after an injection of adrenaline in a dose of 10 µg per kg. A: Control EEG, MV, HB and EKG tracings before adrenaline injection. B and C: EEG, MV, HB and EKG tracings about 20 and 50 seconds after adrenaline injection, respectively. Each calibration is the same order as those obtained in Fig. 1. Time in 1 sec. Note inhibitory changes in amplitude of the MV and bradycardia in the HB and EKG which were observed in C.

Fig. 4. EEG (1. occipito-parietal lead), MV (r. thigh muscles), HB (heartbeat) and EKG (lead II) tracings before and after an injection of noradrenaline in a dose of 10 µg per kg. A: Control EEG, MV, HB and EKG tracings before noradrenaline injection. B and C: EEG, MV, HB and EKG tracings about 20 and 50 seconds after noradrenaline injection, respectively. Each calibration is the same order and those obtained in Fig. 1. Time in 1 sec. Note augmentative changes in amplitude of the MV and HB.

considerably larger dose. With an intravenous injection of noradrenaline in a dose of 30 µg per kg, the MV was observed to cause a somewhat decreased change following an immediate and marked increase in the amplitude of vibration as shown in Figure 3, in which the administration of a moderate dose of adrenaline was found to cause the
inhibitory changes in the amplitude of the MV and heartbeat.

2. Action of adrenaline and noradrenaline on the MV in atropinized rabbits.

In Figure 6 are shown the effects of adrenaline upon the EEG, MV, heartbeat and EKG before and after the administration of atropine sulfate in an adequate dose, which blocks completely the peripheral distribution of the parasympathetic nerves or paralyzes the cholinergic fibers. In the control experiments before the atropine administration, a larger dose of adrenaline (15 µg/kg) was confirmed to cause a considerable inhibitory change in the amplitude and frequency of the MV (Fig. 6 L). Corresponding to the decreased change in the MV, there were also seen the inhibitory changes in the EEG, heartbeat and EKG tracings. A few minutes after the administration of atropine in about 10–15 mg per kg, however, the administration of the same dose of adrenaline as that in the control experiments was observed not to cause inhibitory changes, but facilitatory changes in the MV, EEG, heartbeat and EKG tracings, as shown in Fig. 6 R. In the intravenous injection of noradrenaline into the atropinized rabbits there could also be recognized almost the same effects as those obtained by adrenaline. The above-mentioned results show that the inhibitory effects of adrenaline and noradrenaline on the MV are abolished if the peripheral distribution of the parasympathetic nerves are blocked by an adequate dose of atropine.
3. Action of adrenaline and noradrenaline on the MV in vagotomized rabbits.

In Figure 7 are represented the effects of adrenaline upon the EEG, MV, heartbeat and EKG before and after section of the bilateral vagus nerves in the neck of the rabbit. In the control experiments before vagotomy, a larger dose of adrenaline (15 μg/kg) was confirmed to cause a considerably decreased effect following a transiently increased change in the amplitude and frequency of the MV. There were also seen the facilitatory and inhibitory changes in the EEG, heartbeat and EKG tracings, corresponding to the changes in the amplitude of the MV. After the control experiments, the vagus nerves in both sides of the animal were exposed and cut at the level of the neck. In vagotomized rabbits, the intravenous injection of the same dose of adrenaline as that in the control experiments was seen not to cause the same effects as those observed before vagotomy, but the facilitatory changes in the amplitude of the MV. In the HB and EKG tracings, there were observed concurrently the facilitatory effects caused by adrenaline given in a larger dose, while could not be seen in the EEG tracings. However, there was observed in some cases a slightly decreased change in the MV by the administration of adrenaline in a
larger dose, although not so marked as that before vagotomy. In the cases of noradrenaline, there were observed the same effects as those obtained by adrenaline. Thus, the inhibitory effects of adrenaline and noradrenaline were shown to be abolished completely or sometimes partially when the vagus nerve connections were blocked, as shown in the cases of the administration of atropine as well as of vagotomy. The above-mentioned results show that adrenaline and noradrenaline exert the facilitatory effects on the MV originally in a larger dose than threshold, that is the minimum effective amounts to cause the response.

4. Action of adrenaline and noradrenaline on the MV in rabbits under benzylimidazoline.

In Figure 8 are presented the effects of benzylimidazoline upon the EEG, MV, heartbeat and respiratory movements in the awake and resting rabbit. The intravenous administration of benzylimidazoline (10 mg/kg) was found to cause a decreased change in the amplitude of the MV. In addition to the inhibitory changes of the MV, there were also observed the decreased changes in the EEG, heartbeat and respiratory movement tracings. In Figure 9 are, furthermore, shown the actions of adrenaline on the EEG, MV, heartbeat and respiratory movements in the rabbit before and after the administration of benzylimidazoline. There was provoked no change in the amplitude of the MV by the intravenous injection of a smaller dose of adrenaline (1 μg/
Fig. 8. EEG (1. occipito-parietal lead), MV (r. thigh muscles), HB (heartbeat) and Resp (respiratory movement) tracings before and after the administration of benzylmidazoline. A: Control before an injection of benzylmidazoline. B: About 5 minutes after benzylmidazoline injection in a dose of 10 mg per kg. Each calibration indicates 50 μV for the EEG and 1 mV for the MV, HB and respiratory movements, respectively. Time in 1 sec. Note inhibitory changes in the EEG, MV, HB and respiratory movements which were caused by benzylmidazoline.

Fig. 9. Effect of adrenaline on the EEG (1. occipito-parietal lead), MV (r. thigh muscles), HB (heartbeat) and Resp (respiratory movement) in the rabbit before (L) and after (R) the administration of benzylmidazoline. A: Control tracings before an injection of adrenaline. B: About 14 seconds after adrenaline injection in a dose of 1 μg per kg. C: About 25 seconds after adrenaline. Each calibration shows the same order as that in Figure 8. Time in 1 sec. Note no effect of adrenaline on the MV and HB in the rabbit under benzylmidazoline.

kg), which had been confirmed to cause a facilitatory change in the amplitude and frequency of the MV before benzylmidazoline. In the EEG, heartbeat and respiratory movement tracings, there was not observed such clear changes in the amplitude and frequency. In the cases of noradrenaline, almost the same result as those in the cases of adrenaline could be observed. These findings suggest that the facili-
tatory effect of adrenaline and noradrenaline on the MV can be suppressed by benzylimidazoline, which blocks the peripheral distribution of the sympathetic nerves.

DISCUSSION

It was described by Sugano and Inanaga\(^ {11)} \) that adrenaline, acetylcholine, atropine, pilocarpine, eserine, ergotamine and benzylimidazole provoked no significant change in the amplitude and frequency of the MV in the cat. In addition, Inoue\(^ {13)} \) reported that there was caused no change or a somewhat increased change in the amplitude of the MV in the cat by an injection of adrenaline in the dose of 5—10\( \mu \)g per kg, whereas slightly decreased change of the MV by acetylcholine injection in the dose of 10 \( \mu \)g per kg. In their investigations, however, there were recognized no consistent effects of adrenaline upon the MV.

In my experiments mentioned above, on the other hand, detailed studies showed that the intravenous administration of adrenaline or noradrenaline in a smaller dose caused facilitatory changes in the amplitude and frequency of the MV in the rabbit, while the injection of these sympathomimetic drugs in a larger dose provoked the inhibitory changes following transiently increased changes in the amplitude and frequency. In the EEG, heartbeat and EKG tracings, which were recorded simultaneously with the MV, it was observed to cause the facilitatory and inhibitory changes corresponding to the changes of the MV provoked by adrenaline or noradrenaline. The above-mentioned facilitatory and inhibitory changes in the MV were found to be stronger with adrenaline than those with noradrenaline in most cases. Therefore, the inconsistent effects of adrenaline on the MV, which were observed by Sugano and Inanaga\(^ {11)} \), and Inoue\(^ {13)} \), seem to be probably due to whether a larger or smaller dose of adrenaline was administered into animal subjects, although a different species of experimental animals was used.

The facilitatory action on the MV of adrenaline and noradrenaline in a smaller dose is deduced to be due to principally two factors: the one is the augmentative change in muscular components of the MV, and the other the increased change in ballistocardiographic components of the MV. The former is related to the increased tone of the skeletal muscles caused by an injection of adrenaline and noradrenaline, which are known to have a direct action on the brainstem reticular formation. Such a facilitatory effect of adrenaline and noradrenaline as described above, however, might be partly due to the action on the peripheral structures in addition to the center, because it has been recently reported by Toida and Hidaka\(^ {12)} \) that noradrenaline exerts an augmentative effect on the miniature endplate potential and end-plate potential led from the red muscles of the fish. The latter, that is the increased
change in ballistocardiographic components of the MV, seems to be attributed to the increased cardiac output caused by an injection of adrenaline and noradrenaline, which exert an accelerative effect on the pulsation of the heart.

In regards to the inhibitory effect on the MV of adrenaline and noradrenaline in a larger dose, the inhibitory change in ballistocardiographic or muscular components of the MV should be discussed. The ballistocardiographic components of the MV seem to be diminished by the cardioinhibitory and depressor reflexes through the pressor action of adrenaline and noradrenaline on pressoreceptors such as the carotid sinus and arch of the aorta, because there were concurrently observed the markedly decreased changes following transitorily facilitatory changes in the heartbeat as well as the EEG and MV tracings immediately after an injection of adrenaline or noradrenaline. Such physiologic mechanism of the inhibitory effects of adrenaline or noradrenaline, as described above, are shown by the fact that by sectioning the bilateral vagus nerves at the level of the neck, or the administration of atropine in an adequate dose, it decreased completely or partially the inhibitory action of a larger dose of adrenaline or noradrenaline on the MV. According to the recent studies of Ozaki et al.,6) the ballistocardiographic components of the MV were suggested to be accentuated or weakened by cardiac and respiratory changes through facilitatory and inhibitory activity in the autonomic nervous system under various physiological conditions. Awazu1) has recently verified the existence of ballistocardiographic components of the MV by the bio-information processing methods of correlation and frequency analysis. The muscular components of the MV seem to be diminished in amplitude and frequency indirectly through the depressed activitv of the central nervous system, which might be provoked by depressor effects owing to the cardioinhibitory reflex. The facilitatory and inhibitory changes in the EEG pattern corresponding to the change in the amplitude of the heartbeat will accentuate the above-mentioned suggestion also. On the other hand, there has been no report made concerning the inhibitory effect of adrenaline or noradrenaline in a larger dose on the brainstem reticular formation or the nerve-muscle junction, although it was indicated by Bonvallet et al2). that an intravenous injection of adrenaline in the normal cat produced an intense activation of all cortical areas.

It was suggested by Rohracher7) and Yamauchi et al13) that there is a close relationship between the MV and the autonomic nervous system, although a consistent opinion is not always found as to the effect of sympathomimetic and parasympathomimetic drugs on the MV. In my experiments, on the other hand, it has been elucidated that the sympathomimetic drugs, such as adrenaline and noradrenaline, exert a facilitatory action on the MV originally, but these facilitatory effects are inhibited by benzyllimidazoline, known as one of sympatholytic drugs. These
findings seem to accentuate the relationship suggested by Rohracher and Yamauchi et al. Further studies, however, should be performed to clarify the relation between the MV and the autonomic nervous system whose innervation to skeletal muscles has not yet been demonstrated histologically.

The author wishes to thank Prof. T. Ozaki, at whose suggestion this work was performed, for his valuable advice and encouragement.

REFERENCES