Patterns of sympathetic neuron activity associated with Mayer waves

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It has long been known that sustained oscillations of systemic arterial pressure (SAP), with repetition rates of a few cycles per minute and bearing no simple relation to the rhythm of respiratory activity, can be observed in experimental animals under various conditions (27, 20). These oscillations have been usually designated vasomotor, Mayer, or third-order waves (6, 29). On the basis of direct and indirect experimental evidence, it appears that the SAP oscillation is the result of an analogous oscillation of sympathetic neural activity (6, 8, 15, 16, 18). A number of hypotheses have been proposed to explain the mechanism generating such oscillatory sympathetic activity. All these postulate sensory feedback as a prerequisite. However, the experiments performed so far to test these hypotheses have yielded conflicting results (cf. (2) with (3); cf. (15) with (9)). In summary, the problem of the exact nature of the neural mechanism(s) generating the waves and the patterns of sympathetic neuron activity underlying them is still to be settled.

This question has been taken up again in this study, the aims of which were: 1) to describe the CNS processes involved in the generation of Mayer waves in terms of the firing mechanism of the sympathetic preganglionic neuron, and 2) to reexamine the role played by peripheral receptors in the generation of Mayer waves.

**METHODS**

The experiments were performed on 125 adult cats of either sex, weighing 2.1–5.1 kg. Of these, 121 cats were anesthetized with an intraperitoneal injection of sodium pentobarbital (30 mg/kg) followed by intravenous supplements when required. Four cats were decerebrated at the midcollicular level under ethyl chloride-ether anesthesia and then were studied without anesthesia. A tracheostomy was performed on all the animals. Polyethylene catheters were placed in a femoral vein for intravenous injection of drugs and in both femoral arteries (or in one femoral and one common carotid artery) for SAP monitoring and for withdrawing or reinfusing blood. Rectal temperature was monitored and maintained between 36° and 38°C with an infrared lamp. The electrical activity of sympathetic preganglionic units was recorded either from the intermedio-lateral horn of the T1- to T6-cord segments or from strands of the sympathetic cervical nerve. In the first case, a laminectomy was performed between C7 and T3, the dura was split open and retracted, and 3 M NaCl-filled glass microelectrodes (3–4 μ tip diam) were slowly advanced into the cord with a hydraulic microdrive. Sympathetic preganglionic units were identified by their all-or-none, fixed-latency, antidromic action potentials in response to stimulation of the ipsilateral sympathetic cervical nerve (23). The nerve was laid on electrodes and stimulated with 0.1-ms pulses of variable intensity obtained from a Grass SD 9 stimulator. In the second case, a sympathetic cervical nerve was isolated from adjacent structures, cut peripherally, desheathed, and split into fine filaments until only a few active elements were present. The filaments were selected for study only if their activity decreased when SAP was raised (e.g., by the quick intravenous injection of a small amount of blood or saline, or of a dose of noradrenaline of 1–5 μg/kg) and increased when SAP was lowered by bleeding. With the extracellular-microelectrode technique, isolation of single units was easier, but contact with the units was difficult to maintain during the large SAP swings associated with Mayer waves. On the other hand, with the nerve-dissection technique, isolation of single units was more difficult, but the recording was insensitive to SAP variations. The spontaneous respiratory activity was monitored by recording either chest movement with a pneumograph or the electrical activity of the whole phrenic nerve in the neck with a pair of silver electrodes in a pool of paraffin oil. In 12 cats one aortic nerve
was isolated in the neck, cut centrally, and its massed electrical activity recorded with bipolar silver electrodes immersed in a pool of paraffin oil. In three animals bilateral carotid and aortic baro- and chemoreceptor denervation was performed. The carotid sinus regions were denervated by stripping all the surrounding tissue (15). The effectiveness of this denervation was demonstrated by the loss, or great attenuation, of the pressor response to bilateral common carotid artery occlusion. Bilateral cervical vagal and aortic nerve section denervated the aortic receptors as well as all other cardiopulmonary afferents.

In three experiments, a pressure-stabilizing device was used for the elimination of slow SAP oscillations at the repetition rate of Mayer waves without affecting mean pressure. The abdominal aorta was cannulated with a wide-bore Teflon tube just cranial to the origin of the external iliac arteries. The tube was connected to an 8-liter bottle partly filled with heparin-saline solution and pressurized to the animal’s mean arterial pressure. A clamp on the Teflon tube could be released when required, thereby connecting the animal’s arterial system to the bottle. Mayer waves were damped very effectively by this device, while mean pressure and pulse pressure were not significantly affected.

Always in the case of recording from the spinal cord and often when recording from the sympathetic cervical nerve, unilateral or bilateral pneumothorax was performed to minimize movement artifacts due to intrathoracic pressure fluctuations. These animals were paralyzed with intravenous gallamine triethiodide (5 mg/kg) and ventilated with a Harvard respirator.

SAP and spontaneous chest movement were continuously monitored on a Gilson pen recorder. The bioelectric signals were displayed, after suitable amplification and filtering, on a dual-beam oscilloscope, the output of which was led to a gated audio amplifier and speaker. Most data were stored on magnetic tape. Most analyses were done on records obtained by replaying the taped data into a multichannel UV oscillograph (Honeywell Viscorder). Bioelectric signals could be integrated using a gated pulse counter, with reset times between 0.13 and 8.6 s. When phase relationships between integrated electrical activity and other parameters were measured, the delay introduced by the integrator was corrected.

RESULTS

Mayer Waves

In this study, an oscillation of SAP lasting without attenuation for at least 5 min was considered to be an episode of Mayer waves when 1) the repetition rate of the oscillation was independent of, and slower than, the rate of the animal’s respiratory center activity and the rate of artificial ventilation (6, 29), and 2) the SAP oscillation was associated with a simultaneous oscillation of sympathetic neural activity (8, 18).

Thirteen animals exhibited Mayer waves spontaneously (i.e., without any experimental intervention beyond that necessary for the routine surgery). For the others, the procedure used for evoking Mayer waves was the combination of repeated hemorrhage with unilateral or bilateral common carotid artery occlusion. The effectiveness of this procedure has been reported previously by other authors (2, 6, 9, 15–17, 19). On the whole, only 78 of 125 cats (62%) exhibited Mayer waves. Two of these were decerebrate.

Figure 1 summarizes the main properties of the Mayer waves observed in the present series of experiments. Note that the number of episodes analyzed (121) is greater than the number of cats that exhibited Mayer waves due to the fact that some animals presented repeated episodes of Mayer waves separated by periods of steady SAP. When this happened, the characteristics of the waves (period, waveshape, amplitude, mean SAP level) during each episode could be quite different. Figure 1A shows the mean SAP averaged over the fifth full cycle of each episode of Mayer waves Mean SAP ranged from 50 to 200 mmHg with a mean value of 107. The repetition rate of the waves (Fig. 1B), obtained by averaging the intervals between 11 consecutive wave peaks for each episode, ranged from 1 to 7 cycles/min with a mean value of 2.5. The amplitude of the waves was measured as the difference between systolic pressure at the peak and at the trough of the wave and was averaged over 10 consecutive waves for each episode of Mayer waves. The histogram of amplitudes is shown in Fig. 1C. Amplitudes range from 7 to 80 mmHg, with a mean of 27. Figure 1D shows a plot of Mayer wave repetition rates versus wave amplitude. Whereas the waves of lower repetition rate, i.e., 1–2 cycles/min, exhibited both small and large amplitudes, the waves of higher repetition rates, i.e., 4–7 cycles/min, were consistently of small amplitude. In this frequency range the mechanical properties of vascular smooth muscle may be the factors that limit amplitude. Vascular smooth muscle is known to behave as a low-pass filter, i.e., it strongly attenuates neural signals oscillating with a frequency greater than 3–4 cycles/min (28).
Patterns of Sympathetic Preganglionic Neuron Activity Associated with Mayer Waves

Recordings were made from 38 strands of cervical sympathetic nerves and from 121 units from the lateral horn. During control conditions of steady SAP, spontaneously active single units discharged at rates from 1 to 5 spikes/s. Some units had a discharge characterized by an irregularly occurring sequence of action potentials, while others had rhythmic components in their firing consisting of a grouping of spikes with the period of the heart beat and of the phrenic burst. These patterns of sympathetic preganglionic neuron activity have already been described in some detail in two reports from this laboratory (22, 24).

With the onset of Mayer waves, the units characterized by an irregular type of discharge underwent a change in firing pattern consisting of a cyclical alternation of phases of increased activity with phases of decreased activity or complete silence (Fig. 2). The discharge remained irregular, however, when it was present.

The period of such an activity cycle was identical to that of the simultaneously occurring Mayer waves. The firing rate of the units started to increase on the early part of the descending phase of the Mayer wave, well before its trough, and reached its maximum while the SAP wave was on its ascending limb, on the average 9.1 s (range 4-20 s) before the SAP reached its peak. The minimum discharge rate (sometimes zero) was reached at, or shortly after, the SAP peak. The discharge rate started to increase again during the declining phase of the wave.

In strands presenting respiratory modulation of firing prior to the onset of Mayer waves, the modulation persisted after Mayer waves appeared, but underwent a change consisting of a waxing and waning of the number of firings per respiratory cycle. The period of this modulation was the same as that of the Mayer waves (Fig. 3).

Phrenic-synchronous bursts occurring during the rising phase of the SAP wave had the most spikes, while phrenic-synchronous bursts occurring at, or slightly after, the SAP wave peak had the least number of spikes. During the latter phase, one or two bursts could be skipped entirely. Similar behavior was shown by the units exhibiting cardiomodulated activity. Similarly to that already described for the irregularly firing cells, the mean peak discharge rate of all rhythmically firing cells led the SAP peak by an average of 9.9 s (range 2-20 s).

Open Loop Experiments

A number of authors have proposed that Mayer waves might be the result of oscillation in the reflex mechanisms made of arterial chemoreceptors (2) or baroreceptors (14, 15) and sympathetic neurons. This hypothesis was tested with three types of experiments.

Carotid and aortic baro- and chemoreceptor deafferentation. Three animals were deafferented as described under METHODS. All developed Mayer waves when subjected to the routine procedures described in METHODS. These waves were not distinguishable from those elicited in a nondeafferented preparation. This result, which confirms a previous finding of Ferretti et al. (9) obtained in a different experimental situation, suggests that if Mayer waves are the consequence of oscillation in a feedback mechanism involving peripheral receptors, the relevant receptors are not those located in the carotid arteries and in the aortic arch region. However, since there are other peripheral receptors sensitive to SAP and/or blood volume variations (11, 13, 21), the possibility that these other receptors could be the source of the feed-
back maintaining the oscillation is not ruled out by these experiments. Moreover, the relevant receptors could be within the CNS itself (16). To test these possibilities, it is necessary to eliminate the SAP waves themselves. The rhythm of sympathetic-discharge modulation described above, with a period corresponding to that of the SAP oscillation, should disappear if the SAP waves and, therefore, any associated afferent discharge encoding the pressure wave form are eliminated.

SAP stabilization. To eliminate the oscillations of SAP, the pressure-stabilizer device described under METHODS was utilized in 12 trials in 3 cats. Since the oscillations were eliminated without significant change of the mean SAP, it was assumed that with this device the phasic (i.e., Mayer wave related) components of the afferent signals from baro- and chemoreceptors could be greatly reduced or eliminated, while the tonic (i.e., steady pressure related) components of the same signals would be unaffected.

Figure 4 shows a typical result of such an experiment. Discharges were simultaneously recorded from the aortic nerve (thus sampling the information flowing into the CNS through the afferent limb of the reflex loop) and from a small number of sympathetic units from the cervical sympathetic nerve (thus sampling the information leaving the CNS through the efferent limb of the reflex loop) during an episode of Mayer waves. The aortic nerve activity revealed a slow rhythm with a period identical to that of the SAP oscillation. The peak aortic nerve discharge occurred concurrently with the SAP peak. The sympathetic discharge also showed a similar slow rhythm, with the phase relation, relative to the SAP wave, previously described. When the stabilizer bottle was connected to the animal's arterial system (between arrows) the SAP oscillation was practically abolished, while the mean SAP was maintained at approximately the preexisting level. Accordingly, the tonic component of the aortic nerve activity was essentially unaltered, while the slow periodicity at the Mayer wave repetition rate was practically lost. In spite of the lack of a detectable slow periodicity in the afferents, the slow periodicity of the efferents was maintained during the period of steady SAP. Another example of this type of experiment is shown in Fig. 5.

The dominant result of this type of experiment was that the slow rhythm of sympathetic discharge persisted although SAP fluctuations were absent or 80–90% attenuated. However, often the modulation of sympathetic activity at the Mayer wave repetition rate was not as strong during the phase of steady SAP as during the phase of SAP oscillation. Occasionally, the period of the sympathetic rhythm was altered during SAP oscillation. In one case (Fig. 4) the intensity of sympathetic discharge rate modulation was actually greater in the condition of steady SAP than during the immediately preceding period of SAP oscillation.

Alpha blockade. In three animals, the SAP waves were abolished by the intravenous injection of the adrenergic blocking drug phentolamine mesylate (100–300 μg/kg). In addition to abolishing the waves, mean SAP was decreased to low values, e.g., 50–70 mmHg. The activity of sympathetic units was somewhat modified in association with these changes in SAP, but the rhythmic modulation of activity at the Mayer wave repetition rate persisted during the period

![FIG. 4. Effect of Mayer wave damping on sympathetic preganglionic neuron activity. From top to bottom: systemic arterial pressure; integrated aortic neurogram (integration time 1.1 s, increased activity upward); integrated sympathetic cervical neurogram (integration time 4.3 s, increased activity upward). On mounting, this trace was moved to left by a distance corresponding to 4.3 s. Between arrows, stabilizer bottle was opened. Notice loss of a clear Mayer rhythm in afferent nerve and persistence of rhythm in efferent nerve.](http://ajplegacy.physiology.org/)

![FIG. 5. Effect of Mayer wave damping on sympathetic preganglionic neuron activity. From top to bottom: sympathetic cervical neurogram, integrated sympathetic cervical neurogram (integration time 0.53 s), systemic arterial pressure. A, B, and C are consecutive segments of a continuous record. Between arrows, stabilizer bottle was opened. Notice persistence of Mayer rhythm of sympathetic activity in absence of systemic arterial pressure oscillations.](http://ajplegacy.physiology.org/)
of blockade. An illustration of this behavior is shown in Fig. 6. Record A shows the oscillatory behavior of a bundle of preganglionic axons while SAP oscillation is present. Record B was taken after an injection of 200 \( \mu \)g/kg phenolamine mesylate, which followed after several prior injections of the drug, so that a cumulative dose of 0.7 mg/kg had been given in the course of 60 min. While SAP is stable, the oscillation of sympathetic activity persists. In this particular experiment, the blockade started wearing off (as shown by the reappearance of some SAP oscillation) only 1.5 h after record B had been taken.

**DISCUSSION**

Our observations on the activity of single-unit or multi-unit samples of sympathetic preganglionic neurons have shown, confirming earlier observations dating as far back as 1932 (1), that the discharge pattern of these neurons, in the absence of Mayer waves, is characterized by spike generation which is either irregular or rhythmically modulated with the period of the heartbeat and/or of respiration. These basic features of the sympathetic preganglionic neuron discharge seem to be preserved during episodes of Mayer waves, but in this condition the preexisting pattern undergoes a cyclical alternation of facilitation and depression, the alternation having the same repetition rate as that of the Mayer waves (cf. Figs. 2 and 3). In terms of the firing mechanism of the sympathetic preganglionic neuron, this change in firing pattern can be explained by the simple hypothesis that the excitatory synaptic potentials causing threshold crossing and firing are now riding on the top of a slow oscillation of membrane potential, which, by driving the membrane potential toward, and away from, threshold, alternately increases and then decreases the probability of threshold crossing, and thus of firing. The process can be considered similar to the amplitude modulation of radio-frequency waves by an audio-frequency signal. On account of the large SAP swings observed during Mayer waves, it can also be inferred that the activity of a large number of sympathetic preganglionic neurons must be synchronized (the SAP swings would be absent if individual neurons were modulated out of phase with each other). It is likely that this hypothetical slow wave form at the Mayer wave repetition rate is the result of a periodic synaptic excitation and/or inhibition of sympathetic preganglionic neurons by antecedent neurons. An autochthonous generation of the slow wave form by the sympathetic preganglionic neuron itself is not likely because of the high synchronization of the neurons’ activity. Such slow rhythmic variation of the membrane potential of the sympathetic preganglionic neuron is reminiscent of a similar phenomenon, of faster repetition rate, observed in phrenic motoneurons and attributed to a pattern of activity emanating from the respiratory center (12).

From work on the patterning of movement (7), two main theories emerge which possibly could account for the mechanism of generation of this slowly repeating wave form, modulating the excitability of the sympathetic preganglionic neurons: a “peripheral” and a “central” patterning theory. According to the peripheral theory, the timing of the periodic sympathetic preganglionic neuron activity would be dictated by rhythmic variations in the sensory inflow. This inflow would be routed in feedback loops in such a way that, after appropriate time delays in the system (e.g., delays due to vascular smooth muscle response time), it would provide either enhancement or inhibition of the sympathetic neuron activity. According to the central theory, on the other hand, the pattern of sympathetic neuron activity would be specified entirely by CNS mechanisms. Peripheral inputs may still have a role in affecting the details of the output pattern and/or in maintaining the level of central excitability above some threshold value so that the central mechanism may operate (30), but they would not directly produce the rhythm.

In previous work on Mayer waves the peripheral theory has been preferred, even though the available experimental evidence was either not entirely conclusive (2, 3), or could be considered against the theory (9). The results obtained in the present study, however, seem consistent with a central origin of the pattern of sympathetic activity underlying Mayer waves. Such a conclusion is based on two lines of evidence. 1) Elimination of the sensory inputs most suspect of being the afferent components of the feedback loop postulated in the peripheral theory (carotid and aortic baro- and chemoreceptors) did not prevent the appearance of Mayer waves. 2) When the rhythm of afferent discharges...
consequent to the fluctuating SAP was abolished by stabilizing the SAP during periods of Mayer waves or by alpha-adrenergic blockade (another method of producing "open-loop" conditions), the rhythmic activity pattern of the sympathetic units still continued basically unaltered. Even in the cases in which the stabilization procedure did not lead to complete suppression of the waves but only to great attenuation of them (see RESULTS), the rhythmic modulation of sympathetic activity remained practically unmodified in spite of the fact that oscillation of sensory input was greatly decreased (see Fig. 4), suggesting that the modulation is not a direct consequence of the oscillating sensory input. On the basis of the results of the pressure-stabilizing and alpha-adrenergic-blockade experiments, the SAP oscillations themselves, or the resulting fluctuations of blood flow acting on central receptors, can be eliminated as a mechanism of feedback producing the patterned neural activity underlying Mayer waves. A central origin of a similarly patterned sympathetic activity, observed after administration of convulsant drugs in association with SAP waves similar to Mayer waves, was also postulated by Polosa et al. (25, 26).

Aortic baroreceptor discharges during Mayer waves show, as expected, a rhythm of activity with a period identical to that of the SAP waves, and in phase with the latter (cf. Fig 4), the maximum afferent activity being coincident with the peak SAP. If, as suggested above, a central pattern generator is capable of producing the pattern of sympathetic neural activity responsible for the SAP fluctuations, it is interesting to ask what the influence of such a periodic afferent signal might be upon the central "Mayer waves oscillator." It could be completely irrelevant or it could have an additional (facilitative) synchronizing, wave-shape shaping or frequency-controlling influence, without actually being an obligatory component of the rhythm-generating mechanism (cf. 31).

REFERENCES


A final point for discussion concerns how much CNS is required for the operation of the postulated central oscillator generating the rhythm of sympathetic discharge and the consequent SAP fluctuations. Mayer waves have been observed in both decerebrate (results) and spinal (8, 18) preparations. The latter observations suggest that the postulated oscillator needs only the circuitry within the spinal cord in order to function. Furthermore, Beacham and Perl (5), while recording the spontaneous activity of lumbar sympathetic preganglionic neurons in the acute spinal animal, observed cyclical increases in the discharge frequency of these cells. The highest discharge frequencies occurred with a period of about 25 s, which is within the range of periods of the Mayer waves observed in the present experiments. Franz et al. (10), when recording viscerosympathetic reflexes in the acute spinal animal, observed a waxing and waning of the size of the reflex. These fluctuations, indicating an oscillation of reflex excitability, had a period of 20-40 s. Such a period is again within the range of that of Mayer waves. Additional support for a spinal site of generation of the neural rhythm underlying Mayer waves comes from the observation (unpublished data) that repetitive stimulation of the caudal end of the spinal cord cut at T, may result in SAP oscillation similar to Mayer waves. The spinal mechanism probably operates only if there is an adequate level of excitability (produced, for instance, by direct electrical stimulation or by stimulation of afferents), which raises the level of activity in the system to that needed for oscillation. It is not known yet, however, whether these oscillatory phenomena observed in spinal animals are due to sensory feedback or to the operation of a central pattern generator.

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