BARORECEPTORS are nerve endings that respond to deformation or strain of the vessel walls in which they are located. They do not respond to pressure per se because they are not activated by pressure changes in the absence of deformation (Hauss et al., 1949; Angell-James, 1971). Pressure is sensed by the baroreceptors in a multi-step process that includes pressure-mechanical deformation in the vessel wall followed by mechano-electrical transduction in the receptors themselves. The relationship between wall deformation and intravascular pressure is not direct. Wall deformation may be quantified as strain that is calculated from the ratio of the change in wall radius produced by wall stress to the initial unstressed wall radius. Wall stress is calculated as the product of the distending pressure and the radial distance over which it acts divided by the wall thickness. Wall deformation is also viscoelastic in nature, due principally to the elastin, collagen, and smooth muscle present in the vessel wall. When the wall is strained by pressure, the receptor is deformed by an unknown coupling mechanism probably located in the processes described by Krauhs (1979) and presumably viscoelastic, which influences strongly the dynamic response of the receptors. The preceding steps are the mechanical parts of a sequence linking intravascular pressure to receptor discharge. The major components are shown in Figure 1. The remainder of the sequence is electrical in nature and is determined by the electrophysiological properties of the baroreceptor membrane and axon. By analogy with other mechanoreceptors (Terzuolo and Knox, 1971), receptor deformation generates a receptor potential and thus a receptor current which flows outward across the spike-initiating zone thereby producing baroreceptor discharge (Kuffler and Eyzaguirre, 1955) (Fig. 1). Since baroreceptor discharge is slowly adapting (Bronk and Stella, 1935), the most suitable receptor analogies are provided by slowly adapting distortion receptors, e.g., crayfish stretch receptor, rather than by phasic mechanoreceptors, e.g., Pacinian corpuscle. In the latter case the phasic characteristics are determined by a specialized structure, the lamellated capsule (Loewenstein, 1971), whereas specialized structures of this sort are not present in crayfish stretch receptors or aortic baroreceptors although a few lamellated baroreceptors have been identified in the carotid sinus of the rabbit (Dropmann, 1967). The muscle spindle is a much more complicated end-organ, but its coupling to surrounding muscle has been particularly well studied (Fukami and Hunt, 1977) so that it also might provide useful comparisons. In the crayfish stretch receptor, a series of linear transformations link the code of impulses in the receptor's axon during the steady state and the receptor potential (Terzuolo and Knox, 1971). Thus the frequency of discharge is linearly related to the current flowing from the receptor into the spike-initiating zone, and this current is in turn a linear function of the generator potential. If this sequence holds for baroreceptors, then it seems likely that the nonlinear steady state pressure-discharge curve owes its form to the nonlinear pressure-volume relationship of the vessel in which the receptors are located. However, an important nonlinearity due to the electrical properties of the receptors arises at the spike-initiating zone, since its threshold properties act to suppress completely subthreshold generator potentials. Consideration of this sequence is important since it is axonal discharge rather than receptor potential that is recorded experimentally. Receptor potentials cannot be recorded directly because the nerve endings are too small and cannot be visualized. This is unfortunate, for measurements of receptor potential would provide the requisite information concerning mechano-electric transduction.
Not all baroreceptors are the same. Baroreceptors with myelinated axons (MB's) are complex receptor structures, whereas those with unmyelinated axons (UB's) are simpler (Krauhs, 1979). Furthermore, the vessel walls in which arterial baroreceptors are located range from a specialized structure in the case of carotid sinus baroreceptors to a nonspecialized structure in the case of aortic arch baroreceptors. Carotid sinus baroreceptors are found in the lateral wall of a structurally distinctive portion of a medium-sized muscular artery, whereas aortic baroreceptors occur in a region of the aortic arch that does not differ much from its immediate surroundings. It is worth noting that smooth muscle is infrequent in this region of the aorta and is of the Spannmuskeln type which, upon stimulation, produces little if any changes in wall diameter or wall stiffness (Bader, 1964; Dobrin, 1978). This feature could simplify analysis when agents that alter the electrical properties of baroreceptors are used, since their actions on the nearby electrically excitable smooth muscle might be minimal.

Baroreceptors differ not only among themselves, but baroreceptors in hypertensive animals also differ from those in normotensive animals (McCubbin et al., 1956). In hypertension, they always become reset and have a higher operating point; their sensitivity to increments in pressure may be reduced. In established hypertension, these changes have been shown to result from reduced wall distensibility (Kezdi, 1967), but evidence has been accumulating that the changes can occur in the absence of reduced distensibility (Brown et al., 1976; Sapru and Krieger, 1979).

At this point, the question of the importance of baroreceptor function deserves consideration. Baroreceptor function is important because baroreceptors are the first stage in the neural system that regulates blood pressure. The neural control system is the predominant controlling system under ordinary circumstances because it is the only one with sufficient speed to respond to the common perturbations of blood pressure that result from transient stimuli such as emotions, exercise, and eating. The renal, humoral, and tissue autoregulatory systems which also are involved in blood pressure control are too slow to respond effectively to these stimuli. The role of the baroreceptors in blood pressure regulation is demonstrated readily by sinoaortic denervations. These procedures always elevate blood pressure and increase blood pressure lability or variance. The resultant hypertension subsides and there is controversy concerning its persistence (Guyton et al., 1974), with a majority of the evidence favoring persistent hypertension (Scher and Ito, 1978; Alexander, 1979; Touw et al., 1979; Werber and Fink, 1979). This aspect attains greater significance in view of the facts that denervations are always incomplete and that central synapses vacated by denervation may be occupied by sprouting from remaining intact terminals (Raisman and Matthews, 1972).

We now return to the relationship between blood pressure and baroreceptor discharge; as noted, this has mechanical and electrical components. Earlier studies on baroreceptors emphasized the mechanical aspects. In their pioneering investigations, using recordings of the discharge from single axons, Bronk and Stella (1932, 1935) demonstrated slow adaptation to changes in mean arterial pressure and sensitivity to rates of change of pressure. Further insight came from the extensive studies of single units performed by Landgren (1952a, 1952b). He demonstrated the different ranges of steady state pressure-response curves for large and small amplitude spikes, the complexity of adaptation, and the occurrence of postexcitatory depression. Subsequently, it has been confirmed repeatedly that individual pressure-response curves are nonlinear, beginning from a non-zero frequency point at threshold pressure and rising toward an asymptotic maximum discharge frequently along a hyperbolic or near-hyperbolic trajectory (Landgren, 1952a; Brown et al., 1976) (Fig. 2A). An interesting observation was that application of norepinephrine to the wall of the carotid sinus increased small spike discharge but sometimes reduced large spike discharge. Subsequently, it was shown that stimulation of the sympathetics to the carotid sinus of opossum (Koizumi and Sato, 1969) but not cat (Heymans and Neil, 1958) modulated baroreceptor activity. This has led to a comparison with gamma efferent modulation of muscle spindle discharge, but, unlike the latter case, a clear demonstration of sympathetic modulation of baroreceptor sensitivity under...
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Physiological conditions never has been made. Recordings of mass discharge cannot settle this point (Koushanpour, 1973) because two opposite classes of response have already been identified (Landgren, 1952a). In addition, recording of mass discharge has serious technical limitations, including the cancellation effect that occurs when large numbers of fibers are activated asynchronously, extreme sensitivity of the method to small changes in local recording conditions, and relative insensitivity to small fiber discharge. Recently Bergel et al. (1977) have found that norepinephrine can activate carotid sinus smooth muscle and change discharge at a constant wall radius.

Baroreceptor discharge patterns are complex and have been interpreted by a variety of models (Srinivasan and Nudelman, 1972; Christensen, 1967; Clarke, 1968; Franz, 1969), some mainly mathematical and others based on assumed viscoelastic properties. Electrophysiological properties have been treated simply and have not been tested directly; differences between MB's and UB's have not been considered. In what follows, these aspects of baroreceptor function will be emphasized, along with more recent studies on rate sensitivity, resetting, and developmental changes. Much of the information comes from experiments using an in vitro rat aortic arch-aortic nerve preparation (Brown et al., 1976) in which the baroreceptors have similar static properties to those found in vivo (Nosaka and Wang, 1972). There were several reasons for this approach. First, aortic baroreceptors are located in a part of the aorta which does not differ structurally from the rest of the aortic arch. Thus, measurements of pressure, volume, and radius which are averaged over the entire excited segment are likely to be representative of changes near the receptor elements. As suggested earlier, the effects of active contraction of smooth muscle also are likely to be minimal. This is not the case for the carotid sinus where the receptors are located in a segment that differs structurally from the rest of the vessel which is supplied abundantly with smooth muscle. Second, the in vitro approach offers better experimental control of variables, and since the ionic sensitivity of receptor function was of interest, this was an important consideration. Third, the rat was selected because it is a standard laboratory animal in which a variety of hypertensive models have been developed so that mechanisms of baroreceptor resetting could be investigated.

In our experiments, axonal discharge is plotted as the reciprocal of the spike-to-spike interval, and this measurement is referred to as the instantaneous frequency, $F_{\text{inst}}$. Steady state or dynamic measurements of pressure, volume, or radius, and $F_{\text{inst}}$ have been made under a variety of experimental situations. For purposes of analysis, the static and dynamic properties of the vessel wall and axon can be separated readily from those of the receptor and coupling structures. However, distinctions between the latter two often are difficult. Where a response could be predicted on the basis of current information regarding excitable membranes, an Occamistic approach was taken, and unknown effects on the

![Figure 2](http://circres.ahajournals.org/)

**Figure 2** Steady state and dynamic responses of baroreceptors. A: Steady state pressure-response curves for regularly discharging baroreceptors with myelinated axons (●) or with unmyelinated axons (■). The third set of symbols (▲) is for baroreceptors with unmyelinated axons that show an irregular discharge. $F_{\text{inst}}$ is the instantaneous frequency in the steady state produced by the corresponding pressure step. B: Gain or magnitude of frequency characteristics for baroreceptors with myelinated axons (●) and unmyelinated axons (■). Gain is calculated in dB as the ratio of the amplitude of the nervous discharge to the amplitude of the pressure sine wave that produced it and is plotted against log frequency.
couppling structures were neglected. Nevertheless, this does not exclude the possibility of changes in coupling.

Electrophysiological Properties of Baroreceptors

Postexcitatory Depression and an Electrogenic Na+ Pump

A striking example of an instance in which membrane electrical properties are largely responsible for an event attributed previously to mechanical properties is postexcitatory depression (or PED). PED refers to the marked inhibition of baroreceptor discharge following cessation of a step input of pressure (Fig. 3, left panel) and was attributed to mechanical processes such as nonlinear viscoelasticity of the vessel wall (Landgren, 1952a; Franz, 1969). However, PED is abolished immediately by agents that block the membrane Na-K ATPase carrier, e.g., ouabain, Li+, zero K+, or cooling, and is due to an alteration in membrane electrophysiological properties (Saum et al., 1977). Under ordinary circumstances the Na+-K+ exchange often generates a potential difference of a few millivolts across membranes because of the unequal transport of Na+ and K+, usually 3 Na+ for 2 K+. The resulting charge separation or pump current hyperpolarizes the membrane and hence the reference to a membrane electrogenic Na+ pump. When intracellular Na+ rises, pump activity increases and the hyperpolarization also is increased. A period of increased baroreceptor discharge due to a stepwise increase in pressure can be considered as presenting a Na+ load to the pump which, upon removal of pressure, then hyperpolarizes the membrane beyond its pre-step level causing PED. Blockade of the pump mainly affects the receptors since, in the doses used, the agents usually employed have no effect on static vessel wall properties. More recently we have shown, under the same experimental conditions used in the receptor studies, that dynamic properties of the vessel wall also are unaltered (Andresen, Brown, and Wilson, unpublished observation). Hence, pump blockage does not appear to have a discernible action on the scanty smooth muscle present in ascending aorta and aortic arch of the rat. Neither does it have an effect on the collagen, elastin, and ground substance. Regarding the inconsequential actions of aortic arch smooth muscle, further support comes from the fact that application of norepinephrine in concentrations of 10^-5 to 10^-7 M has no effect on wall properties or receptor discharge under our experimental arrangement. Very high concentrations of 10^-3 M were required to alter receptor discharge.

Pump blockage also causes ionic redistribution across cell membranes, but its immediate effects are not due to this. Furthermore, PED cannot result from accumulation of extracellular K+ during repetitive discharge, since excitation due to depolarization would be expected rather than the inhibition

Figure 3  Adaptation and PED. The left panel shows the receptor response as Fm, (top) to a test step input pressure (bottom). A conditioning pre-step of pressure was applied to produce the initial steady state discharge. Adaptation is the fall in discharge from its transient peak value to its steady state value. PED is the marked inhibition of discharge following the return to pre-step pressure. The right panel shows that zero [K+]o, which blocks the electrogenic Na+ pump inhibits PED. The conditioning and test steps had smaller absolute values because zero [K+]o shifts the static pressure-response curves to lower pressure values. Note that on-off adaptation curves in zero [K+]o remain asymmetrical.
that is observed. More direct studies of PED have been made on the much larger crayfish stretch receptor (Nakajima and Takahashi, 1966), and an electrogenic Na⁺ pump mechanism also has been deduced. As Figure 3 shows, the electrogenic pump has very little effect during a pressure step, because the time course of adaptation is not changed by pump blockers (compare the left and righthand panels). A likely explanation is that, during the pressure step, the voltage drop due to pump current across the receptor membrane is shunted by the highly conductive, depolarized membrane. After elimination of PED by blockade of the pump, the remaining transient undershoot following pressure release is much smaller than the transient overshoot following pressure onset and indicates either some asymmetry in viscoelasticity or another membrane basis for the adaptation. One possibility for the latter could be a calcium-induced increase in K⁺ permeability, currently a favorite explanation for a variety of unexplained membrane phenomena, but tests we have made of this hypothesis were negative (Andresen and Brown, unpublished observations).

The electrogenic Na pump reduces the responsiveness of baroreceptors to changes in pressure acting as a form of negative feedback localized to the receptors. Thus increased discharge which is intermittent with pulsatile pressures increases the intracellular sodium concentration [Na⁺]ᵢ and pump activity which tends to hyperpolarize the membrane during diastole and reduce discharge. Whether this provides more stability to the baroreceptor reflex is unknown. In this regard, it would be interesting to determine whether daily variations in blood pressure in glycoside-treated patients are greater than normal.

Ionic Sensitivity of Baroreceptors

The ionic changes we have used do not appear to affect vessel wall properties and are likely to act on either the receptor or its axon. From a functional point of view, distinction between receptor and axon is not crucial. A consideration of the contribution of Na⁺ to the receptor potential of mechanoreceptors using constant field theory (Hodgkin and Katz, 1949; Saum et al., 1977) led to the prediction that a reduction in extracellular sodium ion concentration, [Na⁺]ₒ, should reset baroreceptors and reduce their sensitivity to changes in suprathreshold pressures; this was found to be the case (Saum et al., 1977; Kunze and Brown, 1978; Kunze et al., 1977) (Fig. 4A). Moreover, baroreceptors respond to very small changes in [Na⁺]ₒ. Changes of 5% (about 7 mM) had effects, and such changes are within the physiological range. The same theory also leads to the prediction that an increase of [Na⁺]ᵢ, of as little as 1 mM might have similar effects.

Baroreceptors respond to increases in extracellular potassium ion concentration, [K⁺]ₒ, and changes in extracellular calcium ion concentration, [Ca²⁺]ₒ, as well. Increases in [K⁺]ᵢ, reduce threshold, but the results of reducing [K⁺]ᵢ, are complicated because there are two effects, hyperpolarization due to the K⁺ diffusion potential and depolarization due to inhibition of the electrogenic Na⁺ pump. There is no evidence that a calcium current contributes to depolarization and the effects of changes in [Ca²⁺]ₒ, are attributable to membrane stabilization (Andresen et al., 1979). There is also interaction among these ionic effects, for example, a small reduction in [Na⁺]ₒ, increases threshold, and this effect is en-
hanced considerably when \([\text{Ca}^{2+}]\), is increased simultaneously. The ionic effects on threshold and suprathreshold sensitivity are graded, and, as the \(\text{Na}^+\) results imply, small alterations in electrolyte concentrations, either individually or in combination, may alter baroreceptor function markedly.

Knowledge of baroreceptor reflexes led to predictions that in open-loop experiments, lowering \([\text{Na}^+]\), would elevate the mean arterial pressure or operating point (Fig. 4B), increase the threshold at which the carotid sinus reflex is elicited, and reduce reflex gain or sensitivity. Each of these predictions was confirmed experimentally (Kunze and Brown, 1978; Kunze et al., 1977). An interesting renal response that was not anticipated was also found. The response was a diuresis without an associated natriuresis. The diuresis was pressure-induced, and the absence of natriuresis required the presence of the renal sympathetic nerves; when these were cut, diuresis was accompanied by natriuresis. This raises the possibility that through their \(\text{Na}^+\) sensitivity the baroreceptors or other circulatory mechanoreceptors, such as cardiopulmonary receptors, might be involved in regulation of body \(\text{Na}^+\) and fluid volume. The divalent cations \(\text{Ca}^{2+}\) and \(\text{Mg}^{2+}\) also affect baroreceptor reflexes in a manner that is predicted by their actions on baroreceptors (Kunze, 1979). Thus, increases in concentration increase reflex thresholds and reduce reflex sensitivity. The significance of the present findings to overall body physiology remains to be elucidated because in hypertensive animals, the differences between UB's and MB's are reduced, and from their pressure-response relationships it appears that UB's now may provide a relatively larger share of the input to the CNS. There also are differences between the dynamic responses or frequency-response characteristics of MB's and UB's, and these are dealt with in the next section.

Dynamic Responses of Baroreceptors

Normally the arterial pressure is pulsatile and it has been known, since the original studies of Bronk and Stella (1935), that baroreceptors are rate sensitive. Therefore it is not possible to infer pressure-response relationships under the usual physiological conditions solely from steady state curves such as those shown in Figure 2A. Carotid sinus reflexes, for example, show rate sensitivity (Stegeman and Tibes, 1969; Ead et al., 1952; Scher and Young, 1970; Sagawa et al., 1972). Thus the reflex gain for an equivalent change in steady pressure over the physiological range is less than that obtained with sinusoidal pressure changes. The rate sensitivity could represent a nonlinear response of the central elements in the reflex arc, since the discharge/min of MB's is unchanged with increasing pressure sine wave frequencies (Brown et al., 1978). The situation is made more complicated because the discharge/min of UB's increases at higher frequencies. Results of experiments using phasic and nonphasic patterns of electrical afferent stimulation argue against a nonlinear central response (Douglas et al., 1956a, 1956b) and suggest that the reflex effects are due to recruitment of afferents during sinusoidal stimulation (Angell-James and Daly, 1970).

Earlier studies of the frequency dependence of baroreceptor discharge generally involved analyses in the time domain using the transients elicited by steps of pressure. Pressure steps are limited because they have finite rise times, which, in our system, ranged from 150 to 250 msec; this puts an upper value of about 6 Hz to the frequencies being tested. Similar restrictions also were present in other studies (Srinivasan and Nudelman, 1972; Christensen, 1967; Clarke, 1968; Franz, 1969). An alternative approach is to use pressure sine waves, and some studies of this sort have been done (Angell-James, 1971; Arndt et al., 1975; Franz et al., 1971). However, these studies gave insufficient information on receptor responses at higher frequencies and did not consider differences between UB's and MB's. We therefore extended the earlier studies and compared...
UB's and MB's. It should be noted, however, that the sine wave method also may be constrained at higher frequencies. The number of spikes per cycle is reduced at these frequencies, and this makes it difficult to determine the sinusoidal features of the receptor response. The effect is small on MB's but larger in UB's as a comparison of Figures 2 and 3 of Brown et al. (1978) illustrates.

In our study, we used sine waves of small pressure amplitudes and frequencies over the entire region of interest. The responses followed the principle of superposition so that linear analysis was appropriate. The most striking finding was the marked difference between the frequency response characteristics of MB's and UB's; MB's showed peaking or resonant enhancement at the fundamental frequency for rat heart rate (4 Hz), whereas UB's showed a damped response at all frequencies (Fig. 2B). The amplitude (Fig. 2B) and phase plots (Brown et al., 1978) owe their shape not directly to characteristics of the vessel wall, receptor membrane, or axon, which have much more extended frequency-response ranges, but rather to the arrangement whereby the receptors are coupled to the vessel wall. The differences were attributed to anatomical differences, MB's appearing to be more tightly coupled to the vessel wall than UB's (Brown et al., 1978).

The frequency response can be modeled by a cascade of transfer functions, the first of which gives a complex second-order response and has a differential equation similar to that used in Equation 11 of Franz et al. (1971). However, calculations with this transfer function alone cannot produce the peaking shown by MB's at 4-6 Hz, since they give an amplitude ratio of about 1.1 for frequencies greater than 0.06 Hz. Peaking could be produced by cascading the first transfer function with the simpler transfer function of a second order underdamped system (Fig. 5). The cascaded system accounts for the phase lead at low frequencies and the fall-off in magnitude of about 40 dB per frequency decade and phase lag at higher frequencies. The model also predicts that oscillations in the step response that were expected to be associated with peaking would be difficult to discern, and this was indeed the case. Thus the step response for MB's and UB's would appear to be similar, and the main difference between the two is attributable to differences in the damping factor of the simple second order system. A detailed analysis of these features of baroreceptor function is being prepared for publication (Wilson and Brown, unpublished observations). The cascaded system responsible for the dynamic responses probably is located in the structures that couple the baroreceptors to the vessel wall, since the vessel wall, mechanoreceptor membrane, and the axon have greatly extended frequency responses.

Another interesting finding was frequency-dependent rectification. At higher frequencies, the sinusoidal discharge shut off at the bottom portions of the sine waves. This occurred at pressure levels well above the static threshold and is related to the nonlinear nature of receptor discharge. Thus, when the phasic component of the generator potential that is increased at higher frequencies falls below threshold, discharge ceases and the instantaneous frequency assumes a clipped pattern. The idea that the phasic discharge of baroreceptors indicates that they operate only near threshold therefore needs revision (Arndt et al., 1975).

It seems worthwhile to speculate on some of the possible consequences of the differences in dynamics between MB's and UB's. Justification comes from the fact that knowledge of receptor properties is often very useful in predicting baroreceptor reflex responses. Information concerning frequency or heart rate will be transmitted to the CNS by MB's only, since UB's provide poor feedback in this regard. On the other hand, information about mean arterial pressure is more likely to be transmitted by UB's. However, the number of impulses transmitted per unit time or average frequency by either set of fibers is not strikingly frequency dependent (Brown et al., 1978) so that, if the CNS "reads" impulses per second rather than instantaneous frequency, this prediction may not be borne out. Distinguishing between these possibilities would therefore be important to our understanding of information processing by the neurocirculatory control centers. In this connection, it is of interest that much of the beat-to-beat modulation of heart rate by the aortic nerve in rabbits is thought to be mediated by UB's (Angell-James et al., 1970; Kardor et al., 1975).

### Resetting of Baroreceptors

Resetting occurs under three sets of circumstances: established hypertension (McCubbin et al., 1956; Aars, 1968), early hypertension (Brown et al., 1976), and following acute mechanically induced changes in arterial blood pressure (Krieger, 1976). Resetting of atrial receptors also occurs in hearts enlarged by congestive failure (Greenberg et al., 1973) and in the hearts of spontaneously hypertensive rats (SHR's) (Rickstein et al., 1979) and prob-

**Figure 5** Cascade of two transformations that relate baroreceptor discharge frequency to suprathreshold distending pressures. The relationship is restricted to linear ranges. The first transfer function, $G_1(s)$, is a truncated second-order version of the one used by Franz et al. (1971); the second transfer function, $G_2(s)$ is required to produce peaking at frequencies between 0.06 and 10 Hz. $\omega_0$ is the system's natural frequency, $\alpha$ is the damping factor, $a$ and $b$ are constants, and $s$ is the Laplace transform variable.
ably has similarities to resetting of arterial baroreceptors. (SHR's are the most widely studied animal model of human essential hypertension.) The main difference among the three types is the time period over which the blood pressure has been elevated, ranging from months and years in established hypertension, to a few weeks in early hypertension, to hours in acute resetting. In established hypertension, a multiplicity of mechanisms exist. Thus, reduced wall distensibility and receptor destruction have been demonstrated, and two other possibilities, uncoupling of the receptor from the vessel wall and changes in the receptors themselves, have not been excluded. In the early stages of hypertension in SHR's, changes in the receptors themselves are primarily responsible for resetting (Brown et al., 1976). Partial resetting of baroreceptors in the absence of wall changes also has been shown by Sapru and Krieger (1970). As Figure 6 shows, baroreceptors from 10-week-old SHR's were less sensitive to wall strain than were baroreceptors from 10-week-old normotensive rats (NTR's). At 20 weeks, however, pressure resetting could be accounted for by reduced aortic distensibility and SHR baroreceptors were, if anything, more sensitive to strain. This indicates that the relationship between baroreceptor function and vessel wall properties is not inferred readily, and direct measurement of the variables involved is required.

Two questions raised by the foregoing results regard the nature of the receptor changes and the relationship of these changes to arterial blood pressure. With respect to the first question, it is possible only to speculate at this point on the receptor alterations. An inferred receptor potential can be interpreted using membrane theory (Saum et al., 1977), and, according to this theory, resetting could be attributed to an increase in [Na⁺], an increase in sodium and potassium conductances with the potassium conductance increase dominating, a decrease in sodium conductance, or altered activity of an electrogenic Na⁺ pump (Saum et al., 1977; Blaustein, 1977; Haddy et al., 1978). It seems possible that any one of these mechanisms or several in combination might be involved in early baroreceptor resetting in SHR’s. In fact, a variety of disorders involving Na⁺ and K⁺ have been reported in different tissues of hypertensive animals. Increases in [Na⁺], have been measured in hypertensive vascular smooth muscle (Friedman, 1976). Increased permeabilities to Na⁺ and K⁺ and altered electrogenic Na⁺ pump activity occur in both vascular smooth muscle and red blood cells from hypertensives (Jones, 1973; Postnov et al., 1976). A choice between these possibilities would require measurement of baroreceptor generator potentials directly, a feat as yet unaccomplished.

With regard to the second question, it appears that the development of hypertension is necessary for resetting. Thus, when SHR's are made normotensive from 6 weeks of age, resetting does not occur although the transduction process still does not proceed normally (Andresen and Brown, unpublished observation). Whether resetting is caused by hypertension in a nonspecific manner, or whether SHR baroreceptors are more susceptible to raised blood pressure, remains to be settled. The answer may be provided by testing the effects of acutely raised blood pressure on NTR and treated SHR baroreceptors. This will require consideration of the third type of resetting, namely, acute resetting, first described by Krieger (1976). In these experiments, increases in arterial pressure for periods of 6 hours or less caused a resetting of baroreceptor reflexes toward higher pressures in otherwise normal animals, and the effects were reversible.

Krieger (Michelini et al., in press) has also reported that periods of hypotension reset baroreceptor reflexes so that their thresholds and operating points were lowered, and again the effects were

**Figure 6** Steady state discharge-strain relationships of regularly discharging baroreceptors from normotensive and spontaneously hypertensive rats at 10 and 20 weeks of age. Wall radii were measured with piezoelectric sonomicrometers or optically. Note that the curves for SHR's are not very different between 10 and 20 weeks. However, the NTR curves are much less strain sensitive with maturation—see text for fuller discussion.
reversible, although the recovery times were prolonged compared to the acute hypertensive case. These findings may reconcile the different results of sino-aortic denervation on blood pressure. If, following sino-aortic denervation, the animals are maintained in an environment conducive to lower pressures, the remaining receptors will be more sensitive to increases in pressure and will therefore tend to down-regulate reflex threshold and operating point. If, on the other hand, the animals are in a more stressful environment, the remaining receptors will up-regulate threshold and operating point.

Developmental Changes in Baroreceptors

One of the most interesting and surprising observations to arise from resetting experiments is shown in Figure 6. We found that NTR baroreceptors have less sensitivity to strain at 20 weeks of age than they had at 10 weeks of age (Andresen et al., 1978). This may be of considerable importance in the maintenance of normal blood pressure, since at this age the aorta has become larger and more distensible and, if the baroreceptors did not reset, hypertension might result unless central resetting occurred. An interpretation of the results is that the strain-bearing capacity of baroreceptors somehow is adjusted to the changes in aortic strain that occur during development. The mechanism whereby this might occur is completely speculative, but one simple possibility is that the surface area involved in generating the receptor potential is matched to the distensibility characteristics of the vessel wall in which the receptor is embedded. In any event, this observation is another indication of the flexible relationship that exists between receptors and the vessel walls in which they are embedded. This possibility is implicit in an earlier discussion by Bader (1964) concerning vessel wall changes and baroreceptor function during aging. Thus, with degenerative changes and reduced distensibility, it would be necessary that strain sensitivity of baroreceptors be enhanced for blood pressure to remain at normal levels.

In conclusion, it is clear that more questions have been raised about baroreceptors than answers given. The role of blood pressure in resetting of normal and genetically hypertensive animal models is uncertain. The mechanism for matching receptor function and vessel wall properties during development or aging is unknown. The significance of the ionic sensitivity of the baroreceptors in the regulation of body electrolytes and fluid volume remains to be established, and the reflex consequences of the frequency-dependent differences between MB's and UB's are yet to be determined. A variety of approaches will be necessary to provide the answers to these and other important questions. However one thing seems certain—there are exciting days ahead for investigators interested in baroreceptor regulation of body functions.

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