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Autonomic Origins of Cardiac Responses to Nonsignal Stimuli in the Rat

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Heart rate (HR) and blood pressure responses to nonsignal auditory stimuli were measured in rats after saline or pharmacological blockade of the sympathetic or vagal innervation of the heart. HR responses to the low-intensity stimulus were predominantly deceleratory, whereas responses to the high-intensity stimulus were more notably acceleratory. Both stimuli elicited a biphasic pressor–depressor response, although potential baroreflex influences accounted for only a small proportion of the HR response variance. Deceleratory responses to the low-intensity stimulus were eliminated by scopolamine and thus appeared to be predominantly of vagal origin. Acceleratory response to the high-intensity stimulus appeared to be mediated primarily by sympathetic activation because it was substantially attenuated by the β_1 antagonist atenolol. Furthermore, HR responses to the low-intensity stimulus appeared to reflect coactivation of both sympathetic and vagal systems.

Heart rate (HR) has been widely used as a dependent measure in the study of adaptive responses of an organism to a stimulus or behavioral context. This approach is based on extensive historical and contemporary evidence that documents a close anatomical and functional relationship between central neural mechanisms that mediate behavioral processes and those that regulate internal visceral activities (Brooks, 1981, 1983; Cannon, 1932; Hess, 1957; Obrist, 1981; Papez, 1937; Pavlov, 1927). It is now clear that motivational states as well as cognitive processes such as attention, perception, and learning can have notable manifestations in autonomic nervous system activity (Brooks, 1981, 1983; Coles, Jennings, & Stern, 1984; Lacey & Lacey, 1980; Obrist, 1981; Siddle, 1983). These autonomic manifestations appear to constitute integral aspects of adaptive responses (Brooks, 1981, 1983) and potentially provide objective physiological indexes of behavioral events and processes.

In some cases, the mere appearance or variation in magnitude of an HR response may be sufficient to index a functional reaction (Boysen & Berntson, 1986; Campbell & Ampuero, 1985; Sananes, Gaddy, & Campbell, 1988). More frequently, however, the specific form or topography of the evoked HR response becomes significant in drawing inferences that concern the associated behavioral state. The HR component of the orienting response is generally characterized by cardiac deceleration, whereas defensive or startle responses are typically associated with cardiac acceleration (Berntson & Boysen, 1989; Berntson, Boysen, Baurer, & Torello, 1989; Graham, 1979, 1984; Spinks & Siddle, 1983; Turpin, 1983, 1986). Although exceptions to this generalization have been voiced (Barry & Maltzman, 1985; Dailey, Valtair, & Amsel, 1982), these differential patterns of cardiac response frequently have been used as markers of the nature of the underlying functional reaction. Moreover, differentiations of startle and defensive responses have also been proposed based on the latency, duration, and rate of habituation of the cardiac response (Graham, 1979, 1984; Turpin, 1983, 1986).

In view of the potential use of HR responses as indexes of functional reactions, it becomes especially critical to understand the physiological origin of these response patterns. A notable difficulty in interpreting cardiac responses arises from the fact that HR may not represent a regulatory endpoint but rather may constitute one of many contributors to the adaptive control of circulation (Johnson & Anderson, in press). Sympathetic and parasympathetic systems exert opposing chronotropic influences on the heart, and this autonomic activity is in turn subject to multiple controls. The autonomic control of the heart is critically determined by baroreceptor, chemoreceptor, and respiratory reflexes and hormonal and metabolic conditions as well as central influences arising from systems involved in adaptive response (Brooks, 1981, 1983; Eckberg, 1980; Koizumi & Kollai, 1981; Larsen, Schneiderman, & Pasin, 1986; Nosaka, Nakase, & Murata, 1989; Porges, 1986).

Additional complexities in the autonomic control of the heart arise from recent evidence challenging the traditional view that sympathetic and parasympathetic systems are universally subject to reciprocal central control. Both vagal and sympathetic outflows may be serially activated in phase with cardiac and respiratory cycles (Fagius, Sundlof, & Wallin, 1987; Koizumi, Terui, & Kollai, 1985; Porges, 1986), and concurrent activation of both divisions of the autonomic nervous system may be seen simultaneously under certain conditions (Brooks, 1981, 1983; Iwata & LeDoux, 1988; Koizumi, Terui, & Kollai, 1983). It is also becoming increasingly

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clear that autonomic discharge, even that of the sympathetic system, may not invariably evidence a generalized or pervasive character but may be selectively manifest in particular target organs or even specific vascular beds (Johnson & Anderson, in press).

In view of these complexities, an observed HR change, per se, is relatively uninformative of the central and autonomic events underlying the response. An increase in HR, for example, could result from sympathetic activation, vagal withdrawal, or even a conjoint activation of both divisions. Moreover, such responses could reflect direct activation of central control mechanisms or result secondarily from the dynamic reflexive consequences of more primary cardiovascular adjustments.

The baroreceptor–HR reflex is among the most potent reflexive controls of the heart that operate within the frequency range of cardiac responses to environmental stimuli. This may be of special significance for psychophysiological studies because it is known that environmental events can evoke phasic blood pressure (BP) responses (Iwata & LeDoux, 1988; Lundin, Ricksten, & Thoren, 1984; Obrist, Wood, & Perez-Reyes, 1965). The arterial baroreceptor–HR reflex arises from mechanoreceptors in the carotid sinus and aorta and is manifested by decreases in HR with increasing BP (Spyer, 1981). The baroreceptor afferents terminate mostly in the nucleus tractus solitarius, through which they exert potent control over both sympathetic and vagal activity (Larsen et al., 1986; Spyer, 1981; Strahlendorf & Strahlendorf, 1980). Although HR responses in behavioral contexts can be seen in the absence of BP variation (Obrist et al., 1965), baroreflex controls may significantly contribute to observed changes in HR when pressor or depressor responses are evident.

The central, autonomic, and reflexive controls of the cardiovascular system have been well described in the physiological literature. Unfortunately, these mechanisms have often been examined in paradigms highly disparate from those used in psychophysiological studies. Conversely, although psychophysiological studies are frequently characterized by well-defined behavioral contexts and sophisticated behavioral paradigms, they are sometimes less attentive to the potential physiological origins of cardiovascular responses. Thus, there is a clear need for more substantive conceptual and empirical bridges between these literatures, which would undoubtedly lend depth to both disciplines. Such an approach is exemplified by recent studies of respiratory sinus arrhythmia, which promise a relatively pure index of vagal control of the heart (Porges, 1986; Yongue et al., 1982), and by recent efforts to relate fine-grained changes in HR to the quantitative temporal dynamics of autonomic control (Karemaker, 1985; Somsen, Jennings, & van der Molen, 1988).

Although the literature on the physiological origin of tonic stress-related cardiovascular adjustments is extensive (Grossman, 1983; Johnson & Anderson, in press; Obrist, 1981, 1984; Sherwood, Allen, Obrist, & Langer, 1986; Sudakov, 1981), little is known concerning the origins of phasic cardiac responses to simple signal or nonsignal stimuli. Based on the effects of autonomic blockade in infant rats, Haroutunian and Campbell (1982) suggest that both increases and decreases in HR to environmental stimuli are vagally mediated. The generality of this conclusion, however, may be limited. Under constrained experimental conditions, and with restricted stimulus parameters, one may observe rather simple deceleratory or acceleratory cardiac responses that are associated with orienting and defensive reactions, respectively (Graham, 1979, 1984). In many cases, however, HR responses may be biphasic or polyphasic and likely reflect the dynamic influences of multiple determinants. Obrist et al. (1965) reported that the stimulus-evoked cardiac deceleration arising during classical conditioning in humans could be blocked by the parasympathetic antagonist atropine. During vagal blockade, however, HR responses were not eliminated but reverted to notable cardiac accelerations. This suggests that the experimental stimuli induced concurrent sympathetic activation, which was normally masked by a more potent vagal response. It now appears that conditioned stimuli can induce either reciprocal autonomic responses or coactivation of both sympathetic and parasympathetic controls of the heart in animals (Cohen & Randall, 1984; Galosy, Clarke, Vasko, & Crawford, 1980; Iwata & LeDoux, 1988).

To further clarify these issues, the present study was designed to examine the autonomic and reflexive origins of cardiac responses to nonsignal stimuli in the rat. Experimental stimuli were selected to promote the appearance of both acceleratory and deceleratory responses, and measures of HR as well as BP were obtained during selective pharmacological blockade of the sympathetic and vagal innervations of the heart.

Method

Subjects

The subjects were 28 male Sprague-Dawley rats that were 90–120 days old and that weighed 400–550 g at the time of testing. Animals were maintained on a 12:12-hr light–dark cycle, and food and water were available ad libitum.

Surgical Procedure

A Silastic catheter was surgically implanted during sodium pentobarbital anesthesia (65 mg/kg ip) into the right common carotid artery of each animal for measurement of HR and BP. The catheter device (Vascular Access Port [VAP], Model SLA, Norfolk Medical Products, Skokie, IL) consisted of a septum-covered reservoir and a 13-cm length of Silastic tubing (0.51-mm inner diameter and 0.84-mm outer diameter). A midline incision was made in the ventral cervical region, and the right carotid artery was exposed by blunt dissection. The intact vagus and vagal sheath were carefully separated from the artery. A ligature was secured around the distal portion of the exposed carotid, and an arterial clamp was placed proximally. A small incision was then made in the artery wall, and the catheter was inserted and secured by sutures. After placement of the catheter, a strain-relief loop was left beneath the skin, and the incision was closed in layers. A second incision in the dorsal cervical area allowed for exteriorization of the port, which permitted the animal free movement and prevented dislodging of the device. Another strain-relief loop of catheter was left under the skin on the dorsum, and this incision was sutured around the plastic port collar thereby leaving the septum and collar exposed. Animals were allowed 24 hr to recover before testing.

During and immediately after placement of the cannula as well as two or three times per day thereafter, the catheter was infused with 0.3–0.5 cc of heparinized saline (10 USP units/cc heparin) to maintain patency.

Apparatus

Testing was accomplished in a 51 × 30 × 25 cm chamber that was enclosed in an Industrial Acoustics sound-attenuated room (ambient illumination = 32 lx). For BP recordings, a Huber point needle was inserted into the VAP and linked to a P1000-A pressure transducer (E & M Instruments, Houston, TX) via polyethylene tubing. The transducer was coupled to a Grass Model 7 polygraph (Grass Instruments Co., Quincy, MA) for BP recording, and a microcomputer system simultaneously digitized the data (500 Hz, 12 bit). The recording system was calibrated before each testing session, and a standard pressure pulse was digitized along with the data for each session.

Experimental stimuli were 1 s in duration and were presented by a free-field speaker (frequency response = 50–20,000 Hz, ± 2 db). Stimuli were generated by a solid-state signal generator (500-Hz square wave, 50% duty cycle), and their delivery was controlled by the computer system. Although relatively simple monophasic HR responses may be evoked by selected stimulus parameters (Graham, 1979, 1984), biphasic or polyphasic responses are more typically observed in behavioral contexts. In the present study, we were interested in examining the origin of these more complex patterns of response. Consequently, a square-wave stimulus was used because of its rapid rise time, and stimuli were presented at one of two intensities (55 or 75 db, SPL, at the subject plane) to maximize the likelihood of both deceleratory and acceleratory response components (Graham, 1984; Turpin, 1986).

Pharmacological Agents

To examine vagal contributions to cardiac responses, the muscarinic antagonist scopolamine methyl nitrate was used to block postganglionic parasympathetic receptors. This quaternary compound was used to minimize penetration into the central nervous system (Gilman, Goodman, Rall, & Murad, 1985). In addition, the β_1 antagonist atenolol was used to block the sympathetic neural innervation of the heart. Atenolol was used because of its relative selectivity for cardiac β_1 receptors, the absence of direct effects on myocardial membranes, and its minimal central nervous system actions (Cruickshank, 1980; Frishman, 1979, 1981, 1982; Minneman, Hegstrand, & Molinoff, 1979a, 1979b). Drugs were administered subcutaneously at doses derived from pilot studies and the literature (scopolamine: 0.02, 0.1, and 0.5 mg/kg; and atenolol: 1.0, 5.0, 20.0 mg/kg). Scopolamine was administered in a volume of vehicle equivalent to 0.1% body mass, and atenolol was administered in twice that volume. The saline control vehicle was administered in matched volumes. The noradrenergic α_1 agonist phenylephrine hydrochloride (3 mg/kg sc), which exerts a potent pressor action by virtue of a peripheral vasoconstriction, was used to characterize the baroreceptor–HR reflex. The dosage was selected from preliminary studies to yield pressor responses of 30–50 millimeters mercury (mmHg).

Procedure

Each testing session began with a 15-min adaptation period that was followed by a subcutaneous injection of a pharmacological agent or vehicle solution. After 10 min, a series of six 30-s trials were administered at a variable 120-s intertrial interval (ITI; 105–135 s). Each trial consisted of a 5-s baseline period that was followed by a single stimulus presentation. All stimuli were presented between 10 and 22 min postinjection, which was within the period of asymptotic drug action as determined in preliminary studies.

Subjects were randomly assigned to one of four treatment groups: 2 Drugs (scopolamine or atenolol) × 2 Stimulus Intensities (55 or 75 db, SPL). Each animal received four test sessions, on separate days, which included one test with saline and one with each of the three doses of a given pharmacological agent. Order of dose was counterbalanced across animals. All testing was conducted between 8:00 a.m. and 1:00 p.m.

Baroreflex Procedure

The gain of the arterial baroreceptor–HR reflex was determined in 6 subjects that were catheterized as just described. The testing procedure for these animals consisted of a 15-min adaptation period that was followed by three 30-s preinjection baseline measures (2-min ITI). Immediately after this baseline period, phenylephrine (3 mg/kg sc) was administered, and HR and BP recordings were obtained every 2 min thereafter to follow the change in HR during the increasing pressor ramp. This procedure has been shown to yield gain estimates similar to bolus administrations of phenylephrine (Coleman, 1980). Testing was terminated (a) when BP reached its peak (to minimize confound from potential resetting of the baroreflex; Chapleau, Heesch, & Abboud, 1987; Dorward, Andresen, Burke, Oliver, & Korner, 1982) or (b) if the pressor response exceeded 45 mmHg (to remain within the linear portion of the baroreflex function and to preclude confound from high-threshold cardiac baroreceptors; Faris, Iannos, Jamieson, & Ludbrook, 1980; Head & McCarty, 1987; Ludbrook, 1984). The resulting bivariate data points for each animal (HR and BP) were submitted to a linear regression analysis, and the slopes of the resultant functions were taken as an estimate of baroreflex gain.

Data Analysis

A computer algorithm derived second-by-second measures of mean arterial pressure and beat-by-beat measures of heart period from the digitized data. Artifacts in the heart period data (<1%) were identified and resolved through a visual examination of the raw data together with a computerized artifact algorithm that detected deviant values in the heart period distribution for a given subject (Berntson, Quigley, Jang, & Boysen, in press). Heart period data were then converted to second-by-second rate measures by a weighted averaging of periods that fell wholly or partly within a given second.

Primary evaluation of cardiovascular responses was performed by analysis of variance (ANOVA). As expected, HR responses were often biphasic or polyphasic, entailing both acceleratory and deceleratory components. Consequently, for the overall analyses these responses were quantified by deriving the integral areas under the poststimulus HR time function separately for acceleratory and deceleratory components.[1] A similar approach was applied to the BP responses. All data were then submitted to a between–within mixed ANOVA. A few animals did not complete the entire testing sequence (e.g., due to loss of catheter patency), yielding some missing data (approximately 9%), which was handled using standard methods. Missing values were assigned the cell means, and the degrees of freedom for the error terms of the ANOVAs were adjusted appropriately (Kirk, 1968).

[1] Parallel analyses based on peak acceleratory and deceleratory responses yielded a virtually identical pattern of outcome. The integral values are reported here because they capture a greater proportion of the poststimulus response.

The potential baroreflex contribution to HR was examined on a trial-by-trial basis, through a cross-correlation analysis between the second-by-second changes in mean arterial BP and HR.[2] Because the baroreflex characteristically resets itself around basal BP (Dorward et al., 1982), baseline values were removed, and HR and BP were expressed as a deviation from the mean values for a given trial. This served to eliminate biases related to individual differences in basal cardiac parameters. The bivariate data were then subjected to a cross-correlation analysis (+3 to −3 lags). To further illustrate the potential contribution of the baroreflex to the observed cardiac response, an expected HR response template was derived, based on the baroreceptor–HR reflex. This function was determined for each animal by multiplying the second-by-second pressor response on each trial by the estimated gain of the baroreflex (determined as just outlined). These values were then averaged to provide an overall template of the expected HR response.

Results

Evoked Cardiac Responses

HR responses to the experimental stimuli are illustrated in Figure 1, which depicts the responses over trial blocks under saline control conditions. Because the evoked cardiac responses were often biphasic or multiphasic, the integral acceleratory and deceleratory areas under the poststimulus HR time function were analyzed separately (see Footnote 1). An ANOVA on the integral cardiac acceleration revealed a main effect of stimulus intensity, $F(1, 24) = 8.13$, $p < .008$, reflecting the larger acceleratory responses to the high-intensity stimulus. A Stimulus Intensity × Trial Block interaction, $F(2, 48) = 5.00$, $p = .01$, reflected the selective habituation of the acceleratory response to the high-intensity stimulus. This was in contrast to the emergence and subsequent decline of acceleration over trials to the low-intensity stimulus. An ANOVA on the integral cardiac deceleration revealed a Stimulus Intensity × Trial Block interaction, $F(2, 48) = 3.80$, $p = .028$, reflecting the initial appearance and subsequent habituation of the deceleratory response to the low-intensity stimulus and the emergence of deceleration over trials to the high-intensity stimulus. The origins of these complex patterns of HR response were illuminated by pharmacological manipulations, which will be discussed later. In spite of notable within-session habituation, minimal habituation was apparent over sessions, which was likely attributable to the small number of trials presented. No significant differences were apparent between the integral acceleratory or deceleratory responses on Day 1 versus overall or from the first 2 days to the last 2 days of testing (all $ts < 1.1$, *ns*).

Distinct BP responses were also observed to the experimental stimuli, as illustrated in Figure 1. Data analysis was again based on the integral values of the pressor and depressor components. The general form of the BP response was similar for both stimulus intensities, and the pressor components did not differ significantly between the stimuli. The longer latency depressor components, however, were significantly larger for the high-intensity stimulus, $F(1, 22) = 9.95$, $p = .004$. No significant habituation was apparent in the BP responses, as evidenced by the lack of a main effect of trial block or interactions on this term.

Baroreflex gain. The gain of the arterial baroreceptor–HR reflex was evaluated by the HR change associated with phenylephrine-induced pressor responses in otherwise-untreated animals. As illustrated in Figure 2, the baroreceptor–HR relationship was highly similar across animals, with an average gain (slope) of -1.7 ± 0.1 beats per minute (bpm)/mmHg. This gain estimate was consistent across animals and is generally comparable to previous values reported for the rat (Coleman, 1980; Head & McCarty, 1987).

HR–BP relationships. Because the experimental stimuli evoked notable changes in BP, it is possible that the baroreflex contributed to the observed HR responses. Studies of baroreflex latencies as well as direct neural recordings of autonomic nerve activity in humans and other animals indicate a latency of approximately 0.3–1.5 s for baroreflex manifestations in HR (Coleman, 1980; Fagius & Wallin, 1980; Head & McCarty, 1987; Karemaker, 1985; Koizumi et al., 1985). A cross-correlation analysis between the trial-by-trial HR and BP time functions of the present study yielded results that are consistent with these estimates of baroreflex latency. The analysis revealed a maximal negative cross-correlation between BP and HR at 1 (s) lag (in HR). Although significant, this cross-correlation was low ($r = -.220$, $p < .01$; see Footnote 2), with BP changes accounting for less than 5% of the variance in HR. This low cross-correlation, however, could have resulted from the minimal second-by-second variations in BP over much of the trial epoch, which would maximize the contribution of nonbaroreflex influences. Moreover, slightly different latencies in vagal and sympathetic components of the baroreflex response (Coleman, 1980; Karemaker, 1985; Koizumi et al., 1985) could yield a temporally smeared influence on HR, further diminishing the apparent coupling. In view of these considerations, baroreflex manifestations in HR might he expected to be maximal during more notable and/or prolonged pressure changes, such as those appearing in the immediate poststimulation period. The cross-correlations between BP and HR in the immediate poststimulation period, however, were no greater than the overall values (see Figure 6).

As an alternate illustration of the HR–BP relationship, a template of the potential contribution of the baroreflex to the pattern of HR change can be derived from a linear transform of the BP time functions. Expected templates of the HR response to the low- and high-intensity stimuli were based on the product of the baroreflex gain (as estimated previously) and the observed trial-by-trial changes in BP to

[2] Bertinieri et al. (1985) have used a tangentially related approach to derive baroreflex gain in humans from the slope of the regression function that relates heart periods to instantaneous BP. In this approach, analysis is limited to epochs in which progressive, monotonic changes appear in BP that extend over several heart periods. By using only epochs that show progressive pressure changes, this approach may increase the signal-to-noise ratio by limiting analysis to those periods in which maximal baroreflex variations would be expected. Consequently, we also derived cross-correlations limited to epochs in which monotonic changes in BP were apparent. Although this yielded a slight increase in the cross-correlation coefficients, these differences did not achieve significance. In view of this outcome, the reported results are based on all available data.

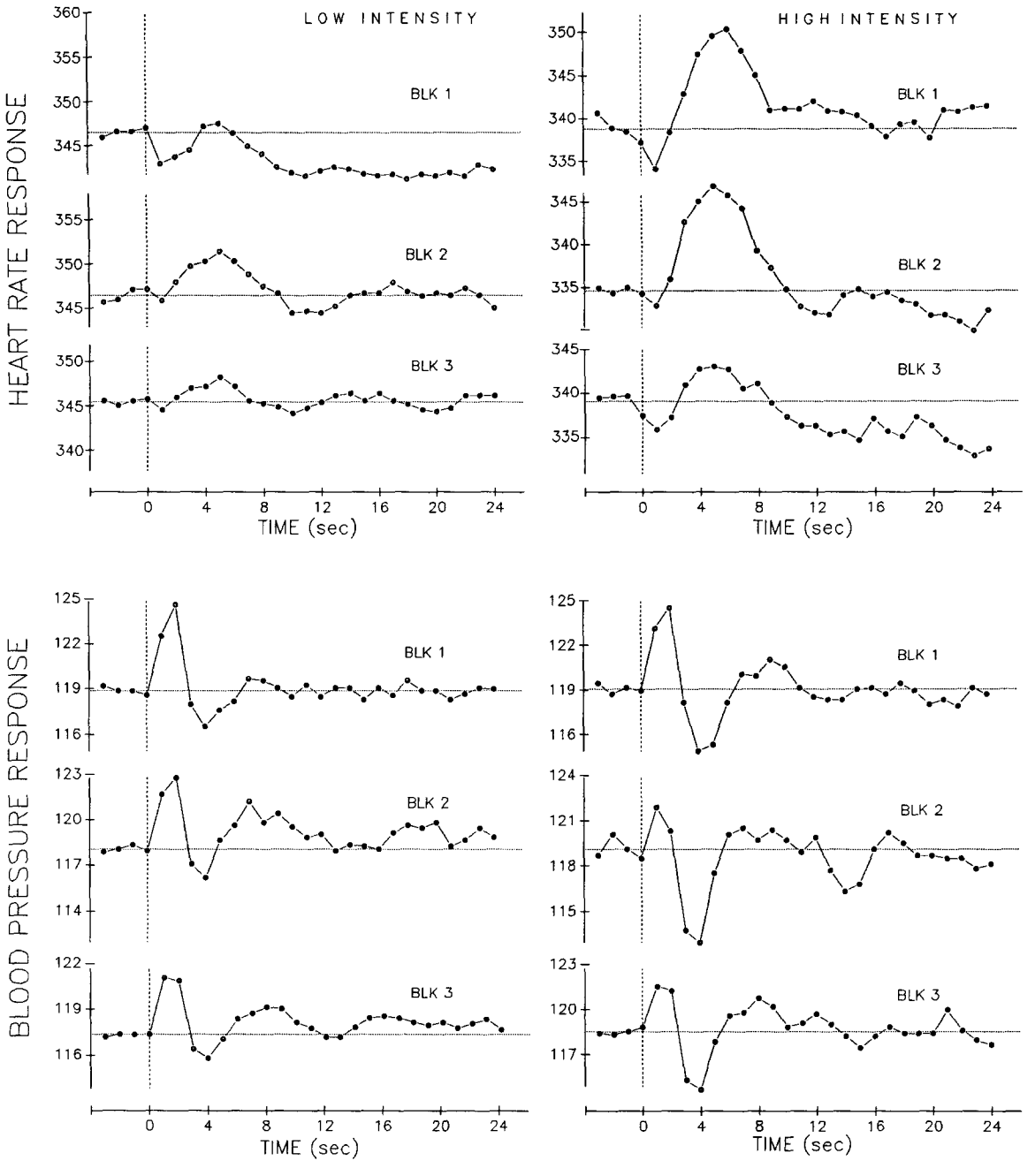

Figure 1. Mean heart rate and blood pressure responses to low-intensity (55 db) and high-intensity (75 db) auditory stimuli under saline control conditions. (Data are illustrated over two-trial blocks [BLK]. Horizontal broken lines illustrate the prestimulus baseline values, and vertical lines delimit the time of stimulus onset.)

the experimental stimuli. Figure 3 illustrates the derived functions (based on 1 lag) for the first trial block, which was representative of other trials. Even though the derived templates were similar in topography to the obtained HR responses, several observations suggest that the similarity may be deceptive. First, the cross-correlations between the predicted and observed HR responses continued to be low (first trial block for the low-intensity stimulus, $r = -.178$, $p < .01$; for the high-intensity stimulus, $r = -.177$, $p < .01$). This was also the case even in the immediate poststimulus period when BP responses were maximal, as indicated by the second-by-second regression coefficients between HR and BP illustrated in Figure 3. Although the overall observed and predicted HR functions were similar, the trial-by-trial variations in HR showed minimal covariation with BP responses.

In addition, notable inflections in the poststimulus HR

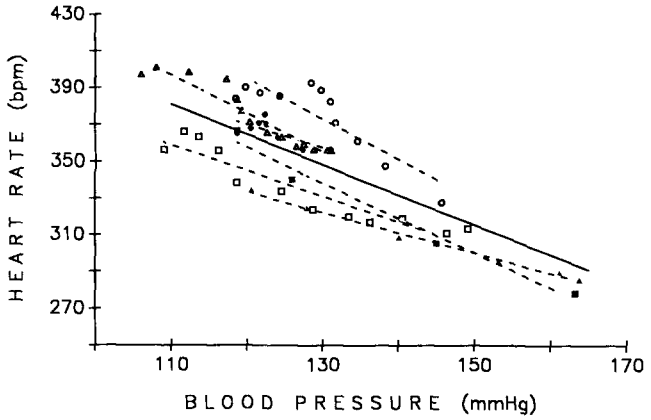

Figure 2. Gain of the baroreceptor–heart rate reflex. (The solid line indicates the mean slope of the heart rate–blood pressure relationship, revealed by the pressor response to phenylephrine. Broken lines show the functions derived from individual animals, which were based on the illustrated data points. bpm = beats per minute; mmHg = millimeters mercury.)

response often preceded, rather than followed, BP changes (see Figure 3). Finally, as is apparent in Figure 1, habituation of HR responses over trials was generally not paralleled by corresponding changes in BP response. Thus, although HR responses were temporally coupled with pressor changes because of the synchronizing effects of the evocative stimuli, these cardiac responses appear to arise predominantly from a central origin other than that of the baroreflex.

Effects of Scopolamine

Baseline measures. As expected, scopolamine yielded a notable dose-dependent increase in baseline HR, $F(3, 26) = 33.94$, $p < .0001$, which achieved asymptotic levels at the intermediate dose (saline = 339.8 bpm; 0.1 mg/kg scopolamine = 418.9 bpm). However, scopolamine induced minimal and nonsignificant changes in BP. The increase in baseline HR would be expected because of the blockade of parasympathetic chronotropic influences on the heart, and the lack of effect on BP is consistent with the minimal parasympathetic influences on the vasculature (Larsen et al., 1986).

Evoked responses. Scopolamine virtually eliminated all deceleratory components of the HR response, with the exception of a late-emerging deceleratory component to the high-intensity stimulus (Figures 4 and 5). These effects were reflected in a significant Dose × Stimulus Intensity interaction, $F(3, 26) = 3.19$, $p = .04$, and a marginal main effect of drug dose, $F(3, 26) = 2.70$, $p = .06$. In contrast, scopolamine did not attenuate acceleratory components and in fact unmasked acceleratory responses, especially on the initial trials of the low-intensity stimulus (Figure 5). Indeed, under scopolamine, the evoked cardiac acceleration to the two stimulus intensities did not appreciably differ. These findings suggest that the low-intensity stimulus may have evoked sympathetic activation, the cardiac manifestation of which was obscured under control conditions by a more dominant concurrent vagal influence.

Although scopolamine elevated baseline HR, this does not appear to account for its effects on stimulus-evoked responses. Based on the law of initial values (Wilder, 1967),

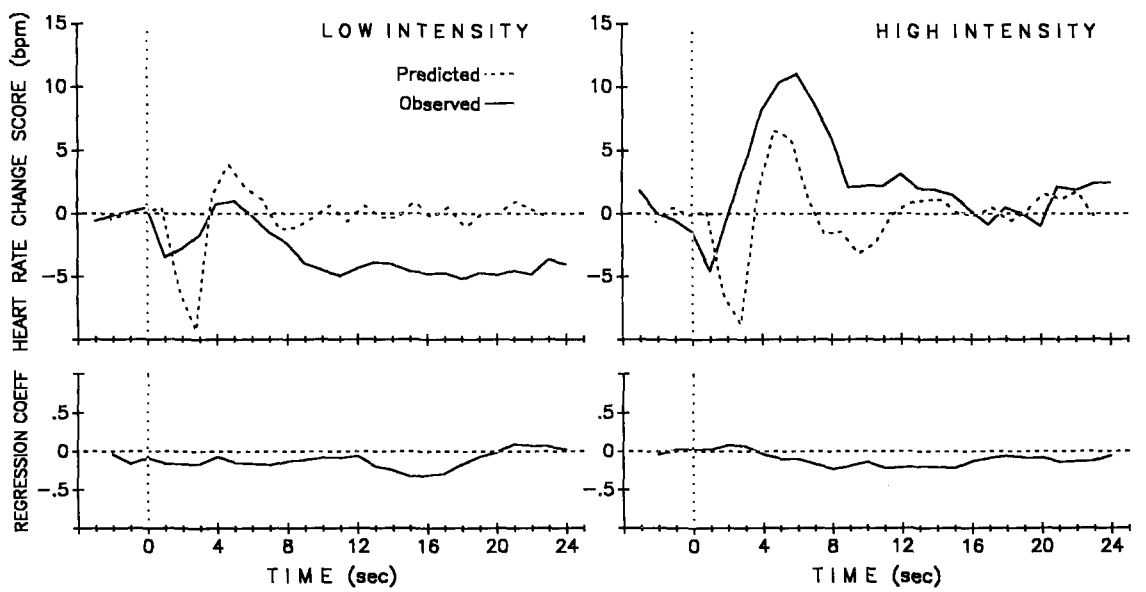

Figure 3. Top panels: Observed heart rate responses, in the first trial block, compared with those predicted by the baroreceptor–heart rate reflex. (Predicted values were derived by multiplying the gain of the baroreflex by the second-by-second changes in blood pressure for each animal. bpm = beats per minute. Bottom panels: Second-by-second regression coefficients [based on 1 lag] for the observed and predicted heart rate functions.)

baseline effects would be expected to increase the magnitude of decelerative responses and attenuate acceleratory components. In fact, just the opposite was observed. Rather, scopolamine appears to have attenuated deceleratory responses by blockade of vagal control of the heart, which in some cases revealed concurrent acceleratory responses of probable sympathetic origin.

In contrast to its effects on HR; scopolamine yielded no significant effects on evoked pressor or depressor responses. At normotensive or hypertensive levels, the baroreflex influence on HR is largely mediated by variations in vagal activity (Coleman, 1980; Head & McCarty, 1987; Stornetta, Guyenet, & McCarty, 1987). Consequently, the blockade of parasympathetic control by scopolamine would be expected to attenuate baroreflex contributions to HR. Consistent with this suggestion, scopolamine eliminated the negative cross-correlation between BP and HR (Figure 6) and, in fact, resulted in a significant positive correlation between these variables (low-intensity stimulus, $r = .280$, $p < .001$; high-intensity stimulus, $r = .220$, $p < .001$). This likely resulted from the concordant vasoconstrictor and positive chronotropic influences of the remaining sympathetic innervation.

Effects of Atenolol

Baseline measures. Atenolol produced a modest decrease in HR, $F(3, 30) = 7.64$, $p < .001$, which also achieved asymptotic levels at the intermediate dose (saline = 345.7 bpm, 5 mg/kg atenolol = 312.5 bpm). This result is consistent with postganglionic β_1 adrenergic blockade of the sympathetic chronotropic influence on the heart. Further consistent with its relative cardioselectivity, atenolol had no significant effects on baseline BP.

Evoked responses. Atenolol significantly attenuated the acceleratory components of the evoked cardiac response (Figure 4). An ANOVA revealed a main effect of drug dose on cardiac acceleration, $F(3, 30) = 6.22$, $p < .002$. The blockade of acceleratory responses by atenolol suggests that these responses were largely of sympathetic origin. In addition, atenolol enhanced the decelerative components of the response to the low-intensity stimulus while attenuating the late-emerging deceleration to the high-intensity stimulus (Figure 5). These effects are revealed by a significant main effect of dose on cardiac deceleration, $F(3, 30) = 4.20$, $p = .013$, and a significant Dose × Stimulus Intensity interaction, $F(3, 30) = 3.96$, $p = .017$. This pattern of results was reciprocal to that of scopolamine and supports the suggestion of a concurrent sympathetic activation evoked by the low-intensity stimulus, which under control conditions served to attenuate a vagally mediated cardiac deceleration. The fact that atenolol blocked the late-emerging deceleration to the high-intensity stimulus (whereas scopolamine did not) further supports the suggestion that this decelerative component may have a sympathetic origin.

Atenolol produced a decrease in baseline HR, which may itself have influenced the observed HR responses. Again, however, the pattern of results was opposite that predicted by the law of initial values.

As anticipated given its relative cardioselectivity, atenolol had no significant effects on BP responses to the experimental stimuli. Sympathetic activation can yield concordant increases in HR as well as in BP, and this direct chronotropic effect is in opposition to expected baroreflex feedback–control of the heart. Consequently, selective blockade of the sympathetic innervation of the heart might be expected to enhance baroreflex controls via the vagus. Accordingly, the cross-correlation between BP and HR was increased by atenolol in relation to saline conditions (Figure 6). This was most apparent for the high-intensity stimulus (cross-correlation under saline, $r = -.233$; under atenolol, $r = -.388$; difference was significant at $p < .01$) but did not achieve significance for the low-intensity stimulus (under saline, $r = -.214$; under atenolol, $r = -.255$). Even under atenolol, however, the baroreflex could account for a maximum of about 15% of the variance in HR responses.

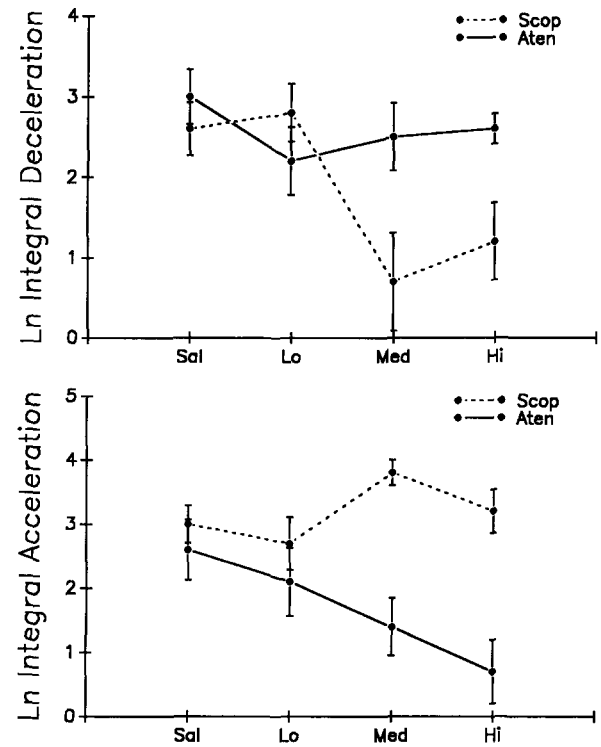

Figure 4. Dose × Response functions for the effects of scopolamine (Scop; 0.02, 0.1, and 0.5 mg/kg) and atenolol (Aten; 1, 5, and 20 mg/kg) on stimulus-evoked deceleratory and acceleratory heart rate responses.

Discussion

Evoked HR responses to the experimental stimuli were comprised of combinations of acceleratory and deceleratory components. Deceleratory HR responses were more prevalent to the low-intensity stimulus, whereas acceleratory components predominated at the higher stimulus intensity. These results are in accord with previous reports and are generally consistent with the purported cardiac features of orienting and defensive responses, respectively (Graham, 1979, 1984; Turpin, 1983, 1986).

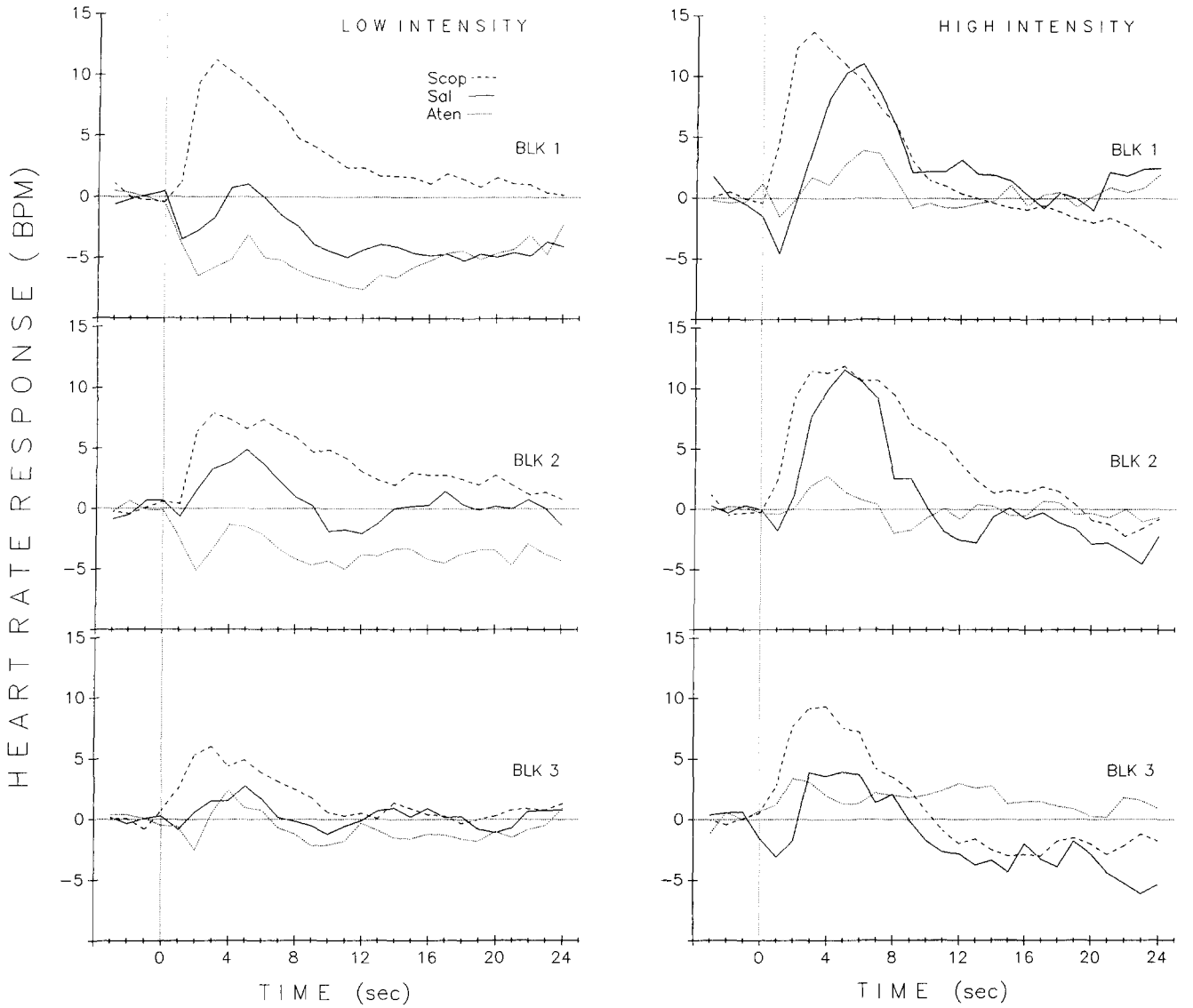

Figure 5. Mean heart rate response to the low-intensity (55-db) and high-intensity (75-db) stimuli after intermediate doses of scopolamine (Scop; 0.1 mg/kg) or atenolol (Aten; 5 mg/kg) compared with the saline (Sal) control. (Data are illustrated over two-trial blocks.)

Evoked BP responses further differentiated between the high- and low-intensity stimuli. The initial short-latency pressor response was equivalent for the two stimuli, whereas the subsequent depressor component was significantly greater at the higher stimulus intensity. In spite of these notable pressure responses, several observations suggest that the baroreceptor–HR reflex was not the predominant determinant of cardiac response. A cross-correlation analysis between BP and HR indicated that BP variations could account for only a modest proportion of the variance in the evoked cardiac response. In addition, notable inflections in the cardiac response function frequently preceded BP responses and consequently could not have been driven by the baroreflex. Finally, BP responses evidenced little habituation, whereas cardiac responses changed considerably over trials.

In view of these considerations, it appears likely that evoked HR responses arose largely from direct central processes, independent of the baroreflex. In fact, at some points, the direction of HR change was opposite that expected from the baroreflex. This is consistent with the report of Obrist et al. (1965) that HR responses to a classically conditioned stimulus in humans are not eliminated by pharmacological blockade of evoked BP responses. The results are also consistent with previous demonstrations of centrally mediated inhibition, or override, of the baroreflex (Gebber & Klevans, 1972; Humphrey, Joels, & McAllen, 1971; Koizumi & Kollai, 1981; Nosaka et al., 1989; Spyer, 1981). Indeed, it is now clear that central influences, including those mediated by limbic–brainstem projections, can enhance, attenuate, or alter the pattern of baroreflex function (Chapleau, Hajduczok, & Abboud,

1989; Nosaka et al., 1989; Pascoe, Bradley, & Spyer, 1989; Spyer, 1981).

Although deceleretory responses were more prevalent to the low-intensity stimulus, and acceleratory responses were more salient at higher intensities, this generalization represents an over-simplification of the temporal features of the evoked cardiac responses. Responses to both stimuli were sometimes biphasic or multiphasic and were subject to notable change over trials. The effects of selective sympathetic and parasympathetic blockade provide insight into the complex origins of the evoked HR responses. Although under some conditions cardiac acceleration may arise from vagal withdrawal (Haroutunian & Campbell, 1982; Katcher et al., 1969), the cardiac acceleration to the high-intensity stimulus in the present study appeared to result primarily from sympathetic activation. Acceleratory responses were largely abolished by the β_1 antagonist atenolol but were unchanged or enhanced by the muscarinic blocker scopolamine.

In contrast, deceleratory responses to the low-intensity stimulus were largely eliminated by the parasympathetic antagonist scopolamine. This is consistent with previous suggestions of a predominant vagal origin of the deceleratory orienting response (Haroutunian & Campbell, 1982; Obrist et al., 1965). However, scopolamine, not only eliminated the cardiac deceleration to the low-intensity stimulus but yielded an opposite acceleratory response. This suggests that the low-intensity stimulus may have produced coactivation of both sympathetic and parasympathetic controls of the heart. In fact, under scopolamine, acceleratory responses to the low-intensity stimulus were highly comparable to those evoked by the more intense stimulus. This is in accord with previous research that suggests that vagal influences can mask or attenuate the cardiac manifestations of concurrent sympathetic activation in behavioral contexts (Iwata & LeDoux, 1988; Obrist et al., 1965). It is also consistent with the finding that atenolol enhanced deceleratory responses to the low-intensity stimulus in the present study. Coactivation of both vagal and sympathetic controls of the heart could also account for the emergence over trials of the modest acceleratory response to the low-intensity stimulus, which may have resulted from a more rapid habituation of the vagal component. This is in accord with previous suggestions concerning the origin of the gradually emerging cardiac acceleration, which is sometimes characteristic of the defensive response to aversive stimuli (Berntson & Boysen, 1989; Graham, 1979, 1984).

Although coactivation was most apparent with the low-intensity stimulus, evidence for an initial vagal response to the high-intensity stimulus can also be seen in the evoked cardiac response (see Figure 5). The initial short-latency cardiac deceleration to the high-intensity stimulus was eliminated by scopolamine, resulting in a more rapid rise of the acceleratory component. Direct recordings of autonomic nerve activity and measures of functional vagal and sympathetic response generally reveal a somewhat shorter latency for vagal influences on the heart (Karemaker, 1985; Koizumi et al., 1985). This has led to suggestions that HR responses occurring within the 1st s or so of an event are likely mediated by the vagus (Karemaker, 1985; Somsen et al., 1988). Results of the present study are generally consistent with this view.

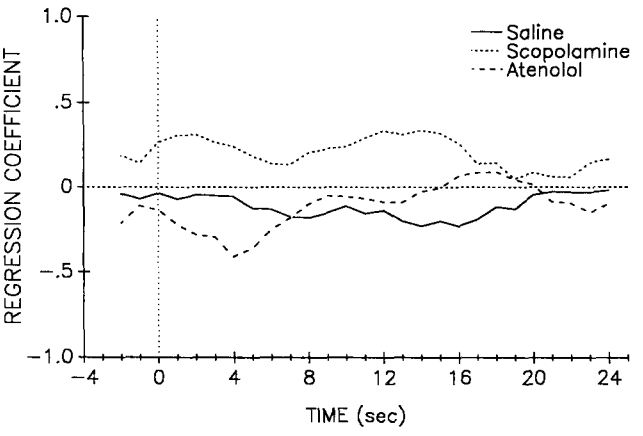

Figure 6. Second-by-second regression coefficients between trial-by-trial variations in heart rate and blood pressure after saline or intermediate doses of scopolamine (0.1 mg/kg) or atenolol (5 mg/kg).

Acceleratory HR responses, of apparent sympathetic origin, were minimal within the 1st poststimulus s and did not peak until 5–6 s after the stimulus. When vagal influences were antagonized by scopolamine, however, acceleratory responses to the high-intensity stimulus were apparent within the 1st poststimulus s. This raises the possibility that short-latency sympathetic effects may be manifested in HR, at least under some conditions.

The apparent coactivation of sympathetic and parasympathetic chronotropic influences on the heart is consistent with recent physiological literature on cardiovascular control (Brooks, 1983; Eckberg, 1980; Koizumi & Kollai, 1981; Koizumi et al., 1983; Kollai & Koizumi, 1979, 1981). Although the functional significance of this coactivation remains to be fully clarified, it may offer an important means of sharpening or focusing autonomic actions, given asymmetries in autonomic control of target organs. Thus, conjoint vagal and sympathetic activation could serve to maximize the predominant sympathetic inotropic influences on the strength of cardiac contraction while minimizing changes in HR (because of the opposing chronotropic influences of vagal and sympathetic systems). Under certain circumstances, this may enhance cardiac output by maximizing time for venous return (Koizumi et al., 1983; Koizumi, Terui, Kollai, & Brooks; 1982). Additionally, coactivation could yield notable sympathetic vasoconstrictor actions on the peripheral vasculature while minimizing exaggerated increases in HR. This could contribute to vasoconstrictor-mediated alterations in regional blood flow, which are known to occur in the absence of appreciable changes in BP (Johnson & Anderson, in press). The potential implications of the concept of coactivation or nonreciprocity in autonomic control clearly warrant further investigation.

The apparent coactivation of vagal and sympathetic systems observed in the present study does not necessarily extend to all stimulus-evoked cardiac deceleration. The square-wave stimulus used in the present study likely contributed to the elicitation of sympathetic components, and pure sine-wave stimuli with slow rise times may more selectively ac-

tivate vagal systems (Graham, 1984). In any event, it is clear that cardiac deceleration, in and of itself, cannot be taken as evidence for the absence of sympathetic activation. Nor does the absence of cardiac deceleration necessarily indicate a lack of vagal activation.

The present data support several conclusions. First, nonsignal stimuli can lead to multiphasic patterns of cardiac response that can arise from joint, and sometimes nonreciprocal, influences of vagal and sympathetic systems. Second, interpretations of complex HR responses to environmental stimuli may be facilitated by appeal to the dynamics of vagal and sympathetic controls. Third, the baroreceptor–HR reflex as well as other cardiovascular reflexes have the potential to significantly contribute to observed HR responses. It also appears, however, that centrally mediated autonomic responses may predominate over baroreflex influences on the evoked cardiac response. These complexities in cardiac control have important implications for psychophysiological studies using HR as a dependent measure and assume special significance for an understanding of complex behavioral–cardiovascular relationships.

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