Heart Rate Reactivity as a Predictor of Neuroendocrine Responses to Aversive and Appetitive Challenges

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The present paper examines the neuroendocrine influences of aversive and reward incentives (noise and shock versus monetary bonuses) presented during reaction time tasks administered to 71 healthy men (ages 21 to 35) classified as being high ($N = 30$) or low ($N = 41$) in heart rate reactivity. High heart rate reactivity was defined as a peak heart rate increase of greater than 19 bpm to a cold pressor test administered on a different day. Independent groups of subjects worked on one of two visual reaction time tasks: either to avoid exposure to noise (115-dBA bursts) and shock (3.5 mV, 2 sec), or to earn monetary bonuses ($0.50). High heart rate reactors showed significant plasma norepinephrine rises from baseline both to aversive incentives and to reward, although they showed significant cortisol responses only during aversive incentives. In contrast, the low heart rate reactors were unresponsive in cortisol and norepinephrine during either type of incentive. These results support psychoendocrine models which view the norepinephrine response as being nonspecifically related to expenditure of effort regardless of the emotional connotations of the challenge, while cortisol is seen as being secreted primarily during periods of distress. The present data further suggest that cardiovascular reactivity is linked to neuroendocrine reactivity, possibly within the central nervous system.

INTRODUCTION

The present study compares the neuroendocrine responses of high and low heart rate-reactive men, measured during work on visual reaction time tasks having either aversive or reward incentives. Cardiovascular and neuroendocrine responses to behavioral stressors are determined in part by the nature of the stressor and in part by the constitutional and psychological dispositions of the individual. Mason (1) had observed in animals that the magnitude of the adrenocortical response to behavioral challenges was determined largely by the degree of aversiveness associated with the task and was apparently not related to the amount of effort or energy expenditure involved. Frankenhaeuser and her colleagues have similarly characterized tasks which involve effort but not distress as affecting primarily noradrenergic secretions, whereas tasks which evoke effort and distress are seen as also affecting adrenomedullary and adrenocortical secretions (2, 3). Under these formulations, the degree of threat associated with a given task would be a determinant of cortisol secretion whereas the amount of effort would be a primary determinant of norepinephrine output.

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Individual differences associated with these neuroendocrine patterns have not been extensively investigated. Our research has focused on cardiovascular responses to behavioral stress and their variation in persons high or low in heart rate reactivity (HRR). In one study, young men classified as high in HRR (determined independently by the magnitude of peak heart rate increase to cold pressor) were also shown to produce larger cardiovascular responses during active avoidance of noise and electric shock than were men low in HRR (4). In a second and third study, high-HRR men were more reactive during work on a visual reaction time task to earn monetary bonuses (5) and during mental arithmetic associated with high-challenge instructions (6). The HRR tendency has been shown by others to be consistent over time (7), concordant in monozygotic twins (8), and to predict atherosclerosis in cynomolgus monkeys (9).

In the present paper, we present an analysis of neuroendocrine data combined from two previously published studies (4, 5). We report that cortisol concentrations were elevated in response to aversive but not to reward incentives, whereas norepinephrine, on the other hand, was elevated during the effort associated with both tasks. Finally, these tendencies were relatively exaggerated among men showing a high degree of HRR and were relatively diminished among men who were low in HRR.

METHODS

Subjects

Seventy-three normotensive, male medical students, ages 21 to 35 years and in good health, took part in the original studies: 29 in the study of reaction time as a means of active avoidance of noise and shock (4) and 44 in the study of reaction time to earn monetary bonuses (5). One subject was unavailable for HRR classification, and no blood samples were obtained from another, leaving a final sample of 71 subjects.

HRR classification. On a day separate from that of the stress procedure, each subject entered the lab for a cold pressor test and signed a consent form approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center and the Veterans Administration Medical Center. Cold pressor was chosen as the challenge for HRR classification because of its lack of similarity to the reaction time task and because it imposes minimal external performance demands.

During this phase, each subject was instrumented for recording of beat-by-beat heart rate, while mean arterial pressure determinations were made by an automated monitor (Critikon, Dynamap, Tampa, FL). The subject sat quietly during a 15-min adaptation period, followed by a 5-min baseline and then a 1-min cold pressor consisting of immersion of the left hand up to the wrist in ice water. Baseline heart rate was the average of the 5-min cardiotachometer output recorded by a Beckman Type R Dynograph (Chicago, IL). HRR grouping was based on the change in heart rate from baseline to the average of the peak 10 sec of response during immersion. Subjects showing 10-sec peak heart rate increases of more than 19 bpm were considered high in HRR and those showing changes of 19 bpm or less were considered low in HRR, based on the median response to the first study (4).

Procedure

On the day of the reaction time task, each subject signed an approved consent form, was instrumented for recording of cardiovascular function (4, 5), and received an intravenous heparinized catheter inserted into a forearm vein to permit repeated blood sampling. The subject then sat in a semirecumbent position for adaptation (15 min), baseline (5 min), task instructions, and the visual reaction time task (15 min).

Tasks

During active avoidance of noise and shock the subject viewed a response light which was illumi-

nated 16 times in 15 min at unpredictable intervals ranging from 4 to 90 sec, with an average intertrial interval of 56 sec. The stimulus on six trials was followed 5 sec later by a 115-dBA white noise burst via earphones and on two trials by a 3.5-mV shock to the shin. The subject was provided with a telegraph key and told that "very rapid" key presses would avoid noise or shock but that slow responses "may or may not" be followed by one of the aversive stimuli. These manipulations had the effect of maximizing uncertainty, equating the amount of aversive stimulation across subjects, and rendering it effectively impossible for the subject to determine that presentation of noise or shock was not contingent on his performance.

During the reward version of this task, a 2-sec response light was presented 60 times during the 15 min at unpredictable intervals ranging from 4 to 26 sec with a mean interval of 15 sec. The subject was instructed to depress the telegraph key as rapidly as possible with his right hand in response to the light, that "rapid" responses would earn a $ 50 bonus, and to try to earn at least 15 to 20 bonuses. A digital counter in front of the subject displayed the number of bonuses earned. To discourage lapses of attention, the subject received an 85-dBA white noise burst via earphones for reaction times greater than 900 msec. This contingency was employed very rarely. The reward criterion was initially set at 270 msec. To ensure continued engagement in the task, if a subject failed to earn a reward in the first 3 min, the criterion was lengthened by 10 msec each trial until a reward was earned. This criterion was then used for the rest of the task.

Blood Sampling

Blood draws were carried out by an experimenter sitting on the opposite side of a screen placed next to the subject's chair. A 21 gauge, intravenous Teflon catheter (Critikon) was attached to a 122-cm intravenous line filled with heparin and fitted with a rubber infusion plug at the far end. Blood was collected into 5-ml Vacutainers (Becton-Dickinson, Rutherford, NJ) prepared with anticoagulant. This system permitted repeated blood sampling with minimal disturbance to the subject. Blood samples were obtained at the end of the baseline and the psychomotor task in both studies. During the rewarded reaction time task, blood was also sampled at the third minute of the task for norepinephrine, and these were averaged with the end-of-task sample to represent a single task value. Cortisol concentrations were assayed using radioimmunoassay (Gamma Coat Kit, Clinical Assays, Cambridge, MA). Norepinephrine was quantified by radioenzymatic assay (Kat-A-Kit, Upjohn Diagnostics, Kalamazoo, MI).

Subjective Responses to Tasks

At the end of baseline and task, the subjects rated their perceived degree of control, stimulation, distress, effort, concentration, tenseness, irritability, tiredness, impatience, boredom, and pleasantness using a series of 10-point, visual-analog scales anchored by the descriptors "least ever felt" and "most ever felt." These scales are adapted from those employed by Forsman (10).

Design and Analysis

The original reports (4, 5) focused primarily on cardiovascular activity in response to the aversive and appetitive incentives. The present analysis was confined to cortisol and norepinephrine concentrations, and to their relationship to reports of subjective states and to HRR. The previously published reports of the separate incentive conditions demonstrated that heart rate response to the cold pressor stimulus generalized to both the aversive and reward versions of the visual reaction time task and predicted a wide range of cardiovascular response differences between the HRR groups including differences in heart rate, cardiac output, and blood pressure (4, 5).

Subjective responses to the two incentive conditions were analyzed in a series of 2 × 2 × 2 Incentive (aversive, appetitive) × HRR Group (low, high) × Period (pre-task, post-task) repeated measures analyses of variance (ANOVAs) conducted on the scales of the subjective states questionnaire. Cortisol and norepinephrine concentrations at baseline and post-task to the two incentive conditions were first analyzed using the above ANOVA design. The pre-task versus post-task cortisol and norepineprine levels were then compared separately for each HRR group under each incentive condition by performing simple effects tests on the Incentive by Group by Period interactions (11). Next, post-task concentrations of these substances were analyzed in a 2 × 2 Incentive by Group analysis of covariance in which post-task concentrations were corrected for pre-task concentrations.

The relationship between heart rates and neuroendocrine activity was examined in a correlational analysis using Pearson's r in which heart rate levels pre-task and post-task, and pre- to post-change scores were correlated with their corresponding cortisol and norepinephrine concentrations.

Two norepinephrine samples could not be analyzed and one cortisol sample was improperly analyzed, leaving a final sample size of 69 for norepinephrine analyses and 70 for cortisol analyses.

RESULTS

Subjective States

Analysis of responses to the 12 scales on the subjective states questionnaire (Table 1) taken before and after the reaction time tasks, revealed that the aversive incentives were experienced as being less pleasant and lower in sense of control, while producing a greater sense of tension, distress, impatience, and irritability ($F > 5.07$, $p < 0.03$). These results suggest that the aversive contingencies were perceived as unpleasant and distressing relative to the reward contingency.[1] The main effects and interaction terms involving the HRR factor were nonsignificant, indicating that the HRR groups perceived the aversive and appetitive contingencies in similar ways.

[1] It will be noted from Table 1 that only distress and pleasantness showed significant interactions from baseline to the respective tasks, with a clear trend for irritability. The primary distinction between mood reports for the two tasks was seen in main effects encompassing baseline and tasks. This may be attributed to the fact that at the end of baseline in both studies, subjects were already fully aware of the contingencies to be employed in the upcoming task. This is likely to have shifted baseline reports of mood states and weakened the tendency for significant interactions to be detected.

Neuroendocrine Responses

Preliminary tests showed that the HRR groups did not differ significantly at baseline in plasma concentrations of norepinephrine, $F(1,65) = 0.77$, NS; or cortisol, $F(1,66) = 0.06$, NS.

Norepinephrine. Plasma norepinephrine concentrations in low and high HRR groups are shown in the *right panels* of Figure 1. Analysis of the norepinephrine concentrations in the HRR groups at baseline and post-tasks showed that the HRR by Period interaction was borderline significant, $F(1,65) = 3.96$, $p = 0.0509$. The high HRRs had higher norepinephrine concentrations following both incentive conditions, relative to their baselines, $F(1,65) = 7.84$, $p < 0.01$ by simple effects tests, whereas the low HRR showed only minimal changes from their baselines to either incentive, $F(1,65) < 1.0$, p = NS. These simple effects tests are reinforced by the analysis of covariance which showed that high HRR had higher post-task norepinephrine concentrations than did low HRR after correction for pre-task values, $F(1,64) = 5.16$, $p < 0.03$. This demonstrates that the effort associated with the performance of the visual reaction time task produced significant elevations in circulating norepineprine regardless of incentive, but that this occurred preferentially in subjects who had shown a tendency toward exaggerated heart rate responses to the cold pressor stimulus.

Cortisol. Cortisol concentrations showed a significant Incentive by Group by Period interaction (Fig. 1, *left*), $F(1, 66) = 10.84$, $p < 0.002$, such that significant pre-task to post-task rises occurred only among high HRRs exposed to aversive incentives. Simple effects tests revealed that cortisol levels did not increase significantly in either HRR group to monetary reward,

TABLE 1. Reports of Subjective States[a]

	Aversive		Appetitive		p Values		
	Base	Task	Base	Task	*E*	Per	*E* × *P*
Tense	3.3	7.6	2.5	6.7	0.008	0.0001	
Distressed	3.1	6.4	2.5	4.6	0.0002	0.0001	0.008
Impatient	3.8	6.3	3.1	5.0	0.008	0.0001	
Irritable	3 2	6.9	2.5	5.0	0.0009	0.0001	0.052
Tired	3.8	3.7	4.2	3.4			
Bored	4.8	3.3	4.9	2.8		0.0001	
Effort	2.4	7.0	2.2	6.3		0.0001	
Interested	3.9	6.3	3.9	6.7		0.0001	
Concentration	3.6	7.8	2.8	7.5		0.0001	
Stimulated	3.3	6.3	3.3	6.5		0.0001	
Pleasant	3.5	2.1	3.3	4.0	0.0001	0.003	0.003
Control	4.6	3.5	4.9	4.5	0.03	0.03	

[a] Entries show mean ratings on visual analogue scales anchored by "Least Ever Felt" and "Most Ever Felt." Units are in cm measured from the "Least Ever" anchor point. Standard errors at baseline range from 0.18 to 0.41 and at post-task from 0.19 to 0.41. All *F* values have 1 and 66 degrees of freedom. *E* = Aversive vs Appetitive, Per = Baseline vs Task.

$F(1,66) < 1.05$, NS. During noise and shock avoidance, cortisol rose significantly among high HRRs, $F(1,66) = 30.10$, $p < 0.0005$, but not among low HRRs, $F(1,66) = 1.71$, NS. Similar results were obtained in the analysis of post-task cortisol concentrations corrected for pre-task values, in which high HRRs showed the greatest concentrations after the aversive incentives, $F(1, 65) = 9.46$, $p < 0.003$. These findings indicate that cortisol was more likely to be elevated in response to aversive circumstances than to those which were rewarding in nature. However, this stimulus-response relationship appeared to be significantly greater among those subjects having a tendency to produce large heart rate responses.

Task Performance

Task performance did not differentiate the high and low HRR groups. In the reward task the groups earned an equivalent number of rewards ($F(1,40) = 1.61$, NS) (4), and in the avoidance task, the respective reaction times were nearly the same (264 vs 262 msec).

HRR

The results presented above suggest a relationship between the tendency toward large HR responses to cold pressor and the magnitude of neuroendocrine responses to the reaction time tasks. We next examined the magnitude of HR and neuroendocrine responses occurring simultaneously during the reaction time tasks. Norepinephrine rises to both tasks were positively related to magnitude of HR change among all subjects, $r\ (68) = 0.24$, $p < 0.05$. Cortisol response was also positively related to degree of HR response, $r\ (69) = 0.47$, $p < 0.0001$. This suggests that the general tendency toward HRR, indexed by the response cold pressor, is not only predictive of neuroendo-

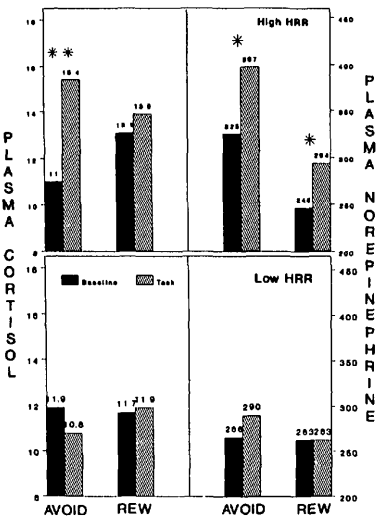

Fig. 1 Mean plasma cortisol (μg/100 ml) and norepinephrine (pg/ml) concentrations following 20 min of rest (baseline) and during a 15-min reaction time task to avoid noxious stimuli (AVOID) or to earn monetary reward (REW). Low HRR = heart rate response of less than or equal to 19 bpm to a prior cold pressor test. High HRR = heart rate response of greater than 19 bpm. *, $p < 0.01$; **, $p < 0.001$.

crine responses to the visual reaction time task, as shown above, but also that the HR responses seen during the task are also positively related to neuroendocrine responses occurring at the same time.

DISCUSSION

The present study is an analysis of psychological and neuroendocrine responses to two visual reaction time tasks, both of which required a high degree of effort and engagement but which differed in the hedonic nature of their incentives. In one case the incentive was avoidance of noise bursts and electric shock and in the other case the incentive was monetary reward. The subjects participating in these separate studies were grouped according to their tendencies to show either large or small heart rate changes (high or low HRR) to cold pressor. The prior reports demonstrated that heart rate change to cold pressor stimulation predicted HRR to both aversive (4) and appetitive (5) incentives along with a range of related cardiovascular variables. The present analysis of these data permits a more direct comparison of the neuroendocrine responses of the high and low HRR groups under strongly contrasted incentive conditions, and the increased sample size permits greater sensitivity to detect differences of interest.

The neuroendocrine responses examined here showed that the efforts associated with the psychomotor requirements of both of the tasks were accompanied by rises from baseline in plasma norepinephrine. On the other hand, cortisol rose significantly from baseline only when the incentives were aversive in nature.

The subjective reports provided by the subjects indicated that both the appetitive and the aversive tasks involved considerable expenditure of effort. Self-reports of effort, interest, tenseness, and concentration increased significantly from baseline in both tasks, and these were among the highest numerical ratings on all scales, suggesting high levels of subjective coping effort. The elements in these ratings correspond to an "Effort" factor previously identified by Lundberg (2). Although the tasks were similar in producing coping efforts, they differed in their reported emotional connotations. The

aversive task was rated as being high in producing feelings of tenseness, distress, impatience, and irritation. These elements figured prominently in Lundberg's (2) "Distress" factor. In addition, the aversive task was rated as low in pleasantness and sense of control.

It should be noted that, in addition to the differences in type of incentive, the two tasks also differed in the number of responses required (16 for noise/shock, 60 for reward), although the difference in number of incentives presented or earned (8 vs 15, respectively) was considerably less. The lower rate of incentive presentation in the aversive task is unlikely to have accounted for the observed enhancement of cortisol response among the high HRRs. The effort expended on the tasks appears equivalent in that each evoked a similar magnitude of norepinephrine response (21% for avoidance, 19% for reward).

These results support and extend earlier theories of the factors determining neuroendocrine responses to behavioral challenge. Mason (1) had observed, in studies with animals, that catecholamine secretions increased to a variety of behavioral manipulations in what appeared to be an effort-related fashion. Cortisol was seen to be released primarily during tasks accompanied by apparent distress or negative affect on the part of the animals. Frankenhaeuser and Lundberg (12) have theorized that distressing tasks may produce rises in cortisol independent of behavioral effort. On the other hand, norepinephrine secretion was thought to be associated with amount of effort regardless of the emotional concomitants of the task in question. Previous research on men undergoing parachute training (13) identified distress-related cortisol responses which diminished with adaptation to the experience of multiple jumps and performance-related factors involving catecholamine secretions which were consistent over many jumps. Cortisol rises were associated with defensiveness and poor performance, whereas catecholamine rises were associated with good performance.

The findings presented here extend such earlier work by indicating that individual physiological reactivity is one determinant of the neuroendocrine component of the behaviors studied. The men who were relatively unreactive in heart rate change to cold pressor were similarly unreactive in norepinephrine and cortisol responses to the reaction time tasks. The high-HRR men clearly accounted for most of the norepinephrine rises seen to both tasks and for most of the cortisol rise to the aversive incentives.

These neuroendocrine response differences between HRR groups appear to derive from a general tendency toward physiological reactivity among high HRRs and do not appear to be secondary to differences in perception of the tasks or to differences in effort indexed by subjective state reports and task performance. This would suggest that the neuroendocrine results were not a function of differences between HRR groups in task perception or degree of motivation, task engagement, sense of mastery, or other effort- or success-related variables.

Therefore, although the psychological and neuroendocrine relationships reported by others are supported by the present results, it appears that the strongest neuroendocrine changes are seen in a subset of physiologically reactive subjects identified by heart rate change to cold pressor. The present emphasis on a physiological interpretation of these results does not preclude the existence of accom-

panying differences in psychological dispositions not assessed by our mood ratings, which were keyed to present-state assessments. Possible interrelationships between physiological reactivity and psychological traits may have played a role in cardiovascular responses to cold pressor as well as to the reaction time tasks. Psychological dispositions have also been shown to predict cortisol responses. For example, Wolff et al. (14) have shown that 17-hydroxycorticosteroid excretion was elevated in parents of children with life-threatening illnesses when the parents lacked adequate defenses in coping with the threat of loss.

Interest in the importance of cardiovascular reactivity has stemmed from a number of sources (9, 15, 16, 17). The idea that reactivity may be seen as a stable constitutional trait gains further support from its greater concordance in monozygotic as compared to dizygotic twins (18) and its consistency over time (4, 7).

In addition to the present results, others have also reported that HRR may predict noncardiovascular responses. Young men at risk for hypertension were shown to reduce their water and sodium excretion to behavioral stress, but only if they were heart rate reactive as well (19). Together with the results reported here, the foregoing suggests that exaggerated cardiovascular reactivity may be associated with altered responses in other systems.

The simultaneous occurrence of large cardiovascular and neuroendocrine responses in the population studied here suggests that these sets of responses may have a common neural basis. In our earlier hemodynamic analyses of these high versus low HRRs, we noted that the HRR groups were similar in vascular resistance, but the high HRRs showed greater heart rate and contractility changes from baseline and a consequently greater increase in blood pressure. Since circulating norepinephrine derives primarily from sympathetic nerve endings proximal to the circulation (20, 21), the greater norepinephrine rises seen in the high HRRs are likely to have been derived from enhanced sympathetic activation of various target tissues with the heart possibly being a major contributor. The cardiac differences between high and low HRRs are, in turn, likely expressions of greater excitability of hypothalamic and medullary centers in the former group. The difference in cortisol response between high and low HRRs to the aversive incentives may also be seen to have a basis in differences in activation of central regulatory centers, since cortisol derives from the adrenal cortex in response to adrenocorticotropic hormone secreted by the anterior pituitary, which, in turn, is produced in response to corticotropic releasing factor produced by the hypothalamus.

Therefore, the enhanced neuroendocrine and cardiovascular responses seen in the high HRR groups may have a common basis in activation of the central nervous system. The fact that self-reports and performance on the tasks were not different between HRR groups argues against cortically mediated factors being the crucial difference, although this does not rule out psychological traits as mediating the reactivity effects seen here. Instead, hypothalamic and medullary control centers in the high HRRs appear to be differentially responsive to apparently equivalent amounts of cortical activation. Differences in hypothalamic and medullary activation are therefore candidates for common physiological mediators of the cardiovascular, catecholaminergic,

and glucocorticoid response differences between these high and low HRRs. This working model of a centrally integrated reactivity tendency is in accord with related work suggesting that cardiovascular responses to mental challenges may be associated with serum lipid levels (22) and that the ratio of total cholesterol to high density lipoprotein cholesterol is positively related to catecholamine responses to mental arithmetic (23).

Questions to be addressed by future research concern how best to view reactivity. It is not yet established whether one or more cardiovascular measures, or one or more neuroendocrine measures, or a combination of these are to be most useful in identifying persons who are reactive to the widest variety of behavioral and physical challenges. In addition, it is not known which index of reactivity, if any, is most predictive of risk of future cardiovascular disease or if different indicators will prove to be predictive of different disease processes involved in hypertension, coronary disease, and arrhythmia.

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