Psychophysiological Reactivity: Mechanisms and Pathways to Cardiovascular Disease

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Objective: This article examines possible sources of heightened psychophysiological reactivity in relation to risk for hypertension and coronary artery disease. The idea that exaggerated reactions to psychological stress may predict greater risk for future disease has some support in the psychosomatic and behavioral medicine literature. However, the pathways by which exaggerated reactivity could arise in a given person and the implications of different sources of reactivity for potential disease relationships have received little attention. **Methods:** This topic is approached through a selective literature review and by means of a neurophysiologically based model of individual differences in physiological reactivity. Temperament characteristics, cognitive processes, neurophysiology, and peripheral physiology are used to indicate three levels that could contribute to exaggerated physiological reactivity. **Results:** At the top level in the model, activity of the frontal cortex and limbic system establish cognitive-emotional sources of activation that may underlie exaggerated physiological reactivity. In the absence of these influences, large responses may be more likely when exaggerated subcortical response tendencies are present via the hypothalamus or brain stem. Finally, peripheral alterations may account for larger reactions in persons who have otherwise normal emotional and hypothalamic and brainstem response tendencies. Cognitive-emotional and hypothalamic-brainstem sources of altered reactivity may cause or aggravate disease. In contrast, altered peripheral reactivity suggests that a pathophysiologic process may be present, serving as a marker for disease. **Conclusions:** These three levels of analysis allow for organization of existing data in the area of cardiovascular reactivity and for planning future studies in a hypothesis-building framework. **Key words:** cardiovascular reactivity, hypertension, coronary artery disease, stress, emotions.

INTRODUCTION

There has long been a belief in physiology and medicine that altered stress reactions may signal the presence of disease or increase the risk of disease. This thinking is reflected in the contemporary *reactivity hypothesis*, which states that persistently exaggerated physical or psychological stress responses can identify individuals or subgroups with an increased risk of cardiovascular disease. Early Greek and Arab physicians noted responses of the heart and blood vessels to emotional events (1). More recently, Walter Cannon (2) proposed to find hidden physiological flaws in prospective aviators by using graded application of altitude stress. In the first explicit application of the reactivity concept, Hines and Brown (3, 4) proposed that exaggerated blood pressure responses to painful ice-water immersion of a hand or foot would reveal a physiologically based risk of hypertension. A strong version of the reactivity hypothesis would view exaggerated responses as causes of disease, whereas a weak version would suggest that such tendencies may signal elevated risk without acting in the chain of causation. Neither version of the hypothesis has received strong support from epidemiological studies or widespread acceptance in the medical literature. However, potential causes of these individual differences in reactivity remain poorly understood, although such an understanding could contribute to critical thinking about putative relationships between reactivity and disease. This article discusses three levels at which the central and autonomic nervous systems might contribute to exaggerated physiological reactivity. We also comment on the use of this information to inform us about whether exaggerated reactivity may play a causal role or act as a marker of elevated disease risk.

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LEVELS OF RESPONSE TO PSYCHOLOGICAL STRESS THAT CONTRIBUTE TO CARDIOVASCULAR REACTIVITY

The physiological pathways that give rise to cardiovascular reactivity differences among persons have not been well specified. This discussion is organized along

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three systemic levels that might account for such individual variation:

I. Reactivity differences may arise at a *cognitive-emotional* level as events are evaluated in consciousness and adaptive behaviors are formulated. This article therefore draws on temperament theory and the neurophysiology of the emotions as a background for understanding how systematic biases at this level may shape physiological responses to stress.
II. Emotional reactions are translated into autonomic or endocrine outputs at the *hypothalamus or brain stem*. Some persons may tend to show greater physiologic arousal for a given psychologic input. In this way even normal emotional reactions could lead to exaggerated responses.
III. *Peripherally altered tissue function* may be a cause of excessive peripheral responses to a challenge even when emotional and brainstem outputs are otherwise normal.

REACTIVITY DETERMINED AT EACH LEVEL MAY INTERACT WITH DISEASE PATHOPHYSIOLOGY

There are mechanisms that plausibly relate altered autonomic and endocrine functions to cardiovascular disease at the tissue level, and it is beyond the scope of this article to describe them in detail. Instead, we broadly indicate some ways in which pathophysiology at the target tissues might alter reactivity in themselves and or how they might interact with changes in endocrine and autonomic signaling from the central nervous system. In the case of hypertension, changes in local autoregulation of blood flow could lead to increased vascular resistance (5), causing a greater response to any acute rise in blood pressure; vascular tissue growth factors, in conjunction with episodes of increased pressure and wall tension, might precipitate exaggerated thickening of the blood vessel wall, leading to permanent increases in peripheral resistance (6); heightened central nervous system responsivity could act on an otherwise normal system to change peripheral structures and their function (7); and heightened central nervous system reactivity could combine with altered peripheral physiology (8) to accelerate the progress of the disorder. In the case of atherosclerosis and arteriosclerosis, several peripheral factors are thought to underlie the disorder at the level of the blood vessel, including vascular wall and endothelial shear stresses interacting with platelet activity (9), altered cortisol rhythms leading to disrupted tissue regulation by peripheral clock genes (10), altered lipid levels, and impaired immune system function (11). These too can interact with altered central nervous system processes to enhance the progression of the disease. These few examples suggest that peripheral changes specific to the disease process can interact with alterations in activational tendencies at higher levels in the system and that both levels can interact in producing altered reactivity in relation to disease. These systems levels are described starting at the top level.

Level I: Exaggerated Cognitive-Emotional Responses

The topmost level in this analysis is the individual's integrated cognitive-emotional responses to challenge, encompassing perceptions, evaluations, and affective responses. These depend on activities of the cortex and limbic system. Cognitive-emotional responses are important contributors to physiological responses. To cause consistent response biases, they should act like traits, being stable over time and across situations. The concept of *temperament* discussed below provides a basis for thinking about origins of consistent reaction tendencies.

From a systems organization viewpoint, brain structures above the hypothalamus form a functional unit that is organized to detect immediate or impending external challenges and to formulate coordinated behavioral and physiological responses to meet them (12). Despite the ability of corticolimbic outputs to affect the activities of lower structures, it is not known if these alone can cause disease in the absence of other risk factors, or what Alexander (13) would have called "organ weaknesses." For this reason, we argue that altered cognitive emotion functions are potential contributors to disease, but they are unlikely to be causes in themselves.

Level II: Heightened Hypothalamic and Brainstem Responsivity

The next systems level controlling peripheral responses encompasses the hypothalamus and brain stem. The brain stem is able to regulate autonomic pathways, and the hypothalamus integrates endocrine functions with autonomic outflow. The ability of exaggerated autonomic or endocrine response tendencies to contribute to disease is controversial, and there is only scant evidence that altered reactivity at this level alone can cause disease (14–16). Schwartz et al. (17) discuss evidence for the role of reactivity in disease pathogenesis in greater detail.

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Level III: Peripherally Altered Tissues

At the peripheral level, abnormal stress responses are recognized as signs of existing disease. In endocrinology, for example, the inability to remove glucose from the blood after a glucose challenge may indicate diabetes. In cardiology, premature fatigue, shortness of breath, exaggerated blood pressure response, or abnormal cardiac rhythm during exercise stress signals the presence of coronary artery disease, hypertension, or autonomic dysregulation. In persons with physical alterations to the blood vessels, such as vascular wall thickening or coronary artery plaque, otherwise normal autonomic and endocrine adjustments to exercise may cause abnormal responses. Exaggerated blood pressure rises during treadmill exercise are a sign of existing or impending hypertension (18–20). Such studies suggest that preclinical alterations in vascular resistance (21) can cause a disproportionate rise in blood pressure relative to an otherwise normal demand for blood flow. In such cases the abnormal reactivity may be an indicator of underlying pathology, thus serving as a marker of disease but not necessarily acting as a cause.

Interrelations Among the Three Systemic Levels Which Influence Reactivity

The three levels at which reactivity differences may be formed are conceptually separable and, to a lesser degree, empirically demonstrable. The value in specifying these is to deconstruct the concept of reactivity into psychophysiologically meaningful elements that have a mechanistic basis and that could plausibly account for how psychological processes may interact with disease mechanisms. The perspective presented below is that tissue-level pathology is necessary for systemic disease to occur, a process necessarily involving level III in our analysis. At level II, systematic alteration of autonomic and endocrine inputs to these tissues can contribute to disease by aggravating existing pathology. Finally, at level I, exaggerated cognitive-emotional activity may contribute to hypothalamic and brainstem biases and tissue pathology when they are present. By implication, activity at higher centers serving thoughts and emotions may act in beneficial ways as well.

It is our hope that systematic consideration of these three levels of function will contribute to progress toward a greater understanding of psychological contributions to health and disease. To make this question manageable, we shall limit our discussion to potential pathways connecting reactivity with coronary artery disease and essential hypertension. Stress exposure may affect both hypertension and atherogenesis in parallel but through different mechanisms. If stress can contribute to these disease processes, it becomes possible to argue that more reactive persons will be more likely to develop cardiovascular disease (15, 16).

LEVELS OF RESPONSE TO PSYCHOLOGICAL STRESS

Psychological stressors are events that challenge the homeostasis of the organism because of their perceived threat value, regardless of potential for physical harm (22, 23). Perceptions and interpretations can influence hypothalamic and brainstem control centers, the outputs of which may alter cardiovascular activity. In turn, the perceptual and interpretive apparatus, especially as these psychological processes are instantiated in the actions of frontal and limbic areas of the brain, may vary across persons in ways that differentially shape the descending activation that determines bodily outputs. Finally, outputs resulting from cognitive-emotional or hypothalamic-brainstem sources can act on effector systems that themselves are capable of abnormal reactions. These sources of differential reactivity have unique characteristics that can be useful in interpreting experimental results.

I. COGNITIVE-EMOTIONAL CONTRIBUTIONS TO INDIVIDUAL DIFFERENCES IN REACTIVITY

A useful approach to characterizing psychological response differences derives from the extensive literature on temperament and the related literature on the emotions. Temperament refers to a person's habitual response style (24). Temperament characteristics (eg, irritability, placidity, shyness, and others) are often manifested from birth and are therefore thought to be biologically based rather than shaped by experience (25, 26). Because temperament allows a neurophysiological instantiation of cognitive-emotional response tendencies, it becomes possible to relate a person's physiological response disposition to characteristic response styles (27). Temperament theory therefore provides a useful body of thought as to the origins of central nervous system bases for cognitive-emotion tendencies that could plausibly function in the necessary way. In turn, differences in central reaction tendencies are accompanied by differences in emotional response, bodily physiologic outputs, or both (28). Temperament therefore provides a conceptual basis for persistent individual differences in person-environment interactions (29), resultant emotional dispositions (30), and altered stress reactivity.

Two lines of animal research provide provocative

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insights into how persons may acquire different temperaments, with consequent lifelong differences in cognitive-emotional response tendencies. Such temperament differences may contribute to differences in reactivity. Both lines of inquiry stem from work initiated by Levine (31), who explored the long-term effects of neonatal experience in rats.

Michael Meaney and colleagues (32) have demonstrated that rats are less fearful and have reduced reactions to stress if raised by mothers who engage in significant nurturing behaviors during the first 10 days of the pup's life. The experience of being nurtured results in increased levels of central serotonin activity that then programs increased expression of a central glucocorticoid receptor gene, leading to higher numbers of glucocorticoid receptors in the hippocampus, amygdala, and prefrontal cortex. This results in enhanced feedback of corticosterone onto the central nervous system throughout the life of the rat. Indeed, females so nurtured also develop into highly nurturing mothers whose offspring also have high levels of glucocorticoid receptors, indicating a behaviorally induced gene expression that is transmitted to the next generation. In human terms, Meaney's studies indicate that highly nurtured rats develop into docile, low-anxiety adults that become nurturing mothers.

In contrast to Meaney's highly nurtured rats, Charles Nemeroff and colleagues (33) are examining untended ones. These pups are separated from their dams for 180 minutes per day during the first 10 days of life. This lengthy separation turns the dams into neglectful mothers who exhibit less nurturing than usual. The pups then show increased central nervous system expression of the stress-inducing peptide, corticotropin releasing factor. They therefore have a highly active hypothalamic-pituitary-adrenocortical axis and elevated sympathetic nervous system function. These rats are highly reactive to the environment and seem to be stress-prone. One of the important distinctions between these nurtured and neglected rats is that they are so different in apparent emotional dispositions, docile in one case and highly reactive in the other. This leads us to thoughts about emotionality in relation to temperament and reactivity in humans.

In both of these models the rats differ from their normal controls in a common set of central nervous system functions that involve prefrontal cortex, anterior cingulate gyrus, and other components of the limbic system. Rats reared by nurturing vs. neglectful dams may therefore be seen as having differences in temperament, a biologically rooted cognitive-emotional tendency to respond to events in a consistent way (34, 35). They provide insights into mechanisms by which temperament is formed and in some cases inherited. Extrapolating to humans, they help us understand how genes and experience can shape high-level central nervous system characteristics that then form a backdrop for variations in reactivity to psychological stress.

Emotion regulation may be a key contributor to childhood temperament and to specific personality dimensions, notably neuroticism and conscientiousness (34, 35). Emotions are complex events that incorporate cognitive, affective, visceral, and motor components. Cognitive-emotion theories regard emotions as states of action readiness that develop when personally relevant events occur (22) and that bias or modulate action potentials (36, 37). The best candidate emotions for promoting reactivity and contributing to disease are considered to be anxiety and anger, as well as a hostile attitude (15, 27, 28, 38–40). Temperament theory, and animal models such as those of Meaney and Nemeroff, suggest that persons may have behavioral and affective response traits based on central nervous system differences (30). This approach therefore provides a plausible psychosomatic basis for reactivity differences deriving from temperament and emotion dispositions.

The discussion above leads to a neurophysiological basis for understanding the power of psychological processes, including interpretations, emotions, and coping efforts to alter systemic activity. Lazarus and Folkman (22) argued that a two-stage appraisal process occurs in which, first, events are evaluated for their threat value, and second, coping resources are weighed against possible threat assessments. This can also be incorporated into a conditioning model in which the evaluation and threat appraisals occur implicitly with less reliance on cognitive underpinnings (23). Thus, emotions shape adaptive behavioral responses, and they bridge the gap from experiences, cognitions, and appraisals to altered endocrine and autonomic outflow. Emotions therefore have components that are *cognitive* (shaping of awareness), *affective* (subjective), *behavioral* (facial expression and posture), and *visceral* (autonomic and endocrine). Emotional reactions that have chronic biases can shape physiological response patterns, and they can be potent enough to precipitate sudden death in a person with underlying coronary artery disease or an arrhythmia-prone myocardium (41).

Cognitive-Emotional Causes of Reactivity Differences in Humans

Schachter and Singer (42) argued that affective experiences are a joint product of autonomic arousal and cognitive labeling. Their emotion studies provide cru-

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cial evidence that conscious processes shape the strength and character of affective and physiological responses. There are two major central nervous system routes by which evaluative activity, and the actions of frontal lobe circuits, participate in forming emotions. The first is the premotor region of the frontal cortex, an area where motor patterns are engaged as preparation for overt behavior, along with the anterior cingulate cortex, a component of the limbic system (43) involved in motor response selection in relation to motivated behaviors. The second is the orbital prefrontal cortex, which is associated with regulation of hypothalamic and brainstem activity in relation to conscious evaluation of events. The orbital cortex is continuous with the ventromedial prefrontal cortex, an area that overlays subcortical structures having extensive dopaminergic and serotonergic terminals, and both are involved with the affective experience of ongoing events (44). Cognitions need to be invested with emotional valence and activation to give experience its affective quality. Damasio (45) discusses the activation of prefrontal circuits in relation to ascending signals from 1) amygdaloid inputs, 2) the bed nuclei of the stria terminalis, and 3) septal regions, all of which come together in proximity to the ventromedial prefrontal cortex (46). At the same time, the amygdala shapes memories by signaling the hippocampus when events have motivational significance, thus altering future behaviors in relation to their adaptive significance (47, 48). This circuitry has been recently reviewed and commented on by LeDoux (49) and Rolls (50). A conceptually similar model of cognition, affect, and autonomic control has been offered by Berntson et al (86).

The higher cognitive-emotional processes described above therefore determine descending inputs to the hypothalamus and brain stem, with resulting modification of endocrine, motor, and visceral response patterning. There is great potential for individual differences in temperament, and cognitive-emotion dispositions, to be linked with persistent changes in the timing, magnitude, and patterning of endocrine responses and visceral outputs via the sympathetic and parasympathetic nervous systems (23, 51, 52).

An example of individual differences in apparently cognitive-emotional response tendencies shaping cardiovascular responses to a social situation is found in a study of high- vs. low-hostile men exposed to mental arithmetic stress and harassment (53). High- and low-hostility groups had equivalent cardiovascular adjustments to mental arithmetic performed under neutral conditions. However, before and during a repetition of this task, the subjects were provoked by a new experimenter who adopted a rude, hostile, uncaring attitude. During the second task administration, the low-hostile men had smaller heart rate and blood pressure responses than before, as though they were adapting to the task repetitions. In contrast, the high-hostile men exhibited greater rises in these measures than before, and afterward they reported substantial feelings of distress, tenseness, and irritation. Although the low-hostile men reported noticing the experimenter's rude behavior, they attributed it to her "having a bad day." In contrast, the high-hostile men expressed resentment toward the rude experimenter with highly personal attributions, such as, "She can't treat me this way."

The two hostility groups had equivalent responses to the affectively neutral task, suggesting that they were similar in physiologically based reactivity to the specific performance demands and global activation associated with the task. In contrast, the greater responses of the high-hostile men after provocation, along with their self-reports, suggest a cognitive and emotional basis for their greater responding in interaction with situational factors (54). If hostile men were simply more reactive to any sort of challenge or to generalized activation, they would have been expected to have greater responses to the neutral task as well. Hostility, when manifested as a consistent trait and a characteristic way of perceiving and reacting to situations, provides an example of the role that temperament may play in shaping responses. Evidence of this sort suggests the potential for cognitive and emotional reaction tendencies to be translated into consistent response differences during daily life.

II. SUBCORTICAL RESPONSES CONTRIBUTING TO REACTIVITY DIFFERENCES

Although the cognitive-emotion model places primary importance on learned and temperamentally based modes of responding, dependent on inputs from the cortex and limbic system, lower brain systems may also play a role in cardiovascular reactivity differences. Examples come from studies in persons at elevated risk for hypertension, whose reactivity differences seem to be unaccompanied by differences in cognitive or emotional responses that might underlie the physiological responses.

This stage of our analysis focuses on inferred differences in reactivity at the level of the hypothalamus and brain stem. However, our ways of challenging the individual in studies of reactivity are usually through exercise, psychomotor performance, or cognitive challenge, all of which call for intentional engagement in a task. To characterize how task engagement, a cognitive process associated with the frontal cortex, might initiate responses at these lower levels, we will make reference to the concept of *central command*. In this

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discussion, the initiating event is assumed to be cortical, but the amplification or gain occurs at the level of the hypothalamus or brain stem, so equal descending inputs may be thought of as resulting in greater or lesser descending outputs in different persons.

In this central command mechanism (55), direct pathways from frontal regions are able to activate hypothalamic and brainstem autonomic control centers (56). Anticipation of exercise can evoke significant peripheral responses in the absence of actual effort; the preparation for a 100-yard sprint causes greater heart rate rises than anticipation of a long-distance run (57). Such central commands are presumed to arise because of conscious preparation resulting in activation of peripheral hypothalamic and brainstem centers. Subjects anticipating exercise therefore manifest a top-down form of cardiovascular activation (23). However, this mechanism differs from the cognitive-emotional one described above, in which the groups differed in psychological traits and the strength of their acute emotional reactions. Central commands per se are activational in nature and not affectively biased. In the three-level model presented here, if two groups of subjects are found to have different cardiovascular responses to an equivalent demand, such as exercise or a video game, under relatively neutral conditions, we might argue that their response differences began at a level below the cortex and limbic system. The examples below therefore rely heavily on self-reports that are comparable between high- and low-reactivity groups.

An application of this central command concept is found in a prospective study of cardiovascular disease in Finland. Apparently healthy men had blood pressures taken while sitting on a bicycle ergometer in anticipation of an exercise stress test (58). Men with higher blood pressures during the anticipation period had greater 4-year blood pressure elevations (58), left ventricular masses (59), and carotid artery arteriosclerosis (60) than the low-pressure reactors. The anticipatory nature of these blood pressure responses indicates the role of central activation in shaping peripheral responses and points to the potential value of examining reactivity to psychological challenges as a predictor of future disease. However, the absence of self-report data limits our information about the source of the differences between high- and low-reactivity persons. Whether conscious appraisals or nonconsciously stimulated elevations in pressure were at work, we can safely say that the greater pressures in the men with subsequent disease were not peripheral changes that arose in response to the effort of exercise but instead were due to some initial input at a higher level in the system.

Other examples of altered hypothalamic and brainstem functions underlying reactivity differences come from studies of adrenocortical response in relation to stress and painful stimulation. In the first example, subjects with borderline hypertension and normotensive control subjects with a negative family history entered the laboratory on four occasions (61). Each time, they were extensively instrumented for cardiovascular monitoring, had a venous catheter placed in a forearm vein, and rested quietly during a baseline period. Afterward a blood sample was collected for cortisol measurement. In the control group, baseline cortisol levels remained low across all 4 days. Among the subjects with borderline hypertension, baseline cortisol was elevated on days 1 and 2, finally matching the lower values of the control subjects only on the third and fourth days. Notably, the groups' self-reported perceptions and emotional reactions to the situation were similar on each of the days, suggesting that the cortisol reaction in the subjects with borderline hypertension was not secondary to consciously perceived activation or threat. In the same study, the subjects were also exposed to mental arithmetic and reaction time tasks, and the cortisol reactions were greater in the subjects with borderline hypertension than in the control subjects (62). Self-reported affect and arousal were sensitive to the tasks, but again they showed no differences between groups. For these reasons it seems that the cortisol elevations of the subjects with borderline hypertension were due to relatively enhanced limbic and hypothalamic outputs in response to the implicit threat of being in a novel experimental setting and to the moderately aversive nature of the tasks, without conscious differences in their perceptions of the situation as inferred from self-reports.

Studies of nociception in hypertension risk converge on a similar conclusion. Normotensive subjects who are at high risk for hypertension report less pain than do control subjects when exposed to a cold pressor test (63) or mechanical compression of a finger (64). Reduced pain sensitivity is also associated with enhanced cardiovascular reactivity in relation to hypertension risk (65). The difference in pain sensitivity is not due to apparent psychological causes as measured by personality tests (64) or scales of anticipatory activation or distress (63). Reports of pain quality showed that high-risk subjects differed from low-risk subjects in the perceived sensory quality of the pain but not in its affective impact (63), again suggesting that the pain-rating differences were not due to personality characteristics or psychological processes that might lead persons to rate equivalent pain in different ways.

McCubbin and Bruehl (66) have shown that hypertension risk is accompanied by high levels of central opioid activity. The greater pain tolerance in hypertension risk groups may reflect higher central opioid lev-

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els, resulting from deficient negative feedback of peripheral opioids (66) or from increased activation of the hypothalamic-pituitary-adrenocortical axis, leading to increased secretion of β-endorphin. The greater adrenocorticotropin and cortisol release seen in high-risk persons would be accompanied by greater amounts of β-endorphin because these molecules are released by the pituitary simultaneously in equal amounts (67–70). High levels of cortisol release would therefore predict lower nociception due to concomitantly greater release of β-endorphin (71). In either case, the antinociception of the hypertension risk subjects suggests a hypothalamic and brainstem process that is apparently not caused by descending psychological influences.

In these examples, cardiovascular and endocrine responses were greater in the high-risk and borderline hypertension groups than in the low-risk groups, but perceptions of the situations and affective responses did not seem to differ. In particular, the heightened responses seem to have arisen at a stage after these subjects had formed their situational evaluations and emotional responses but before they generated peripheral responses. Potential sources of these reactivity differences are therefore inferred to be at the level of the hypothalamus and brain stem.

III. PERIPHERAL SOURCES OF DIFFERENCES IN REACTIVITY

Although we may often look to central nervous system determinants of differences in reactivity, it is possible that in some instances persons are more reactive because of alterations in peripheral mechanisms. In this case a person might have exaggerated responses to a stressor without any alteration in appraisals, emotions, or centrally induced alterations in endocrine or autonomic outflow. For example, persons may cluster into groups on the basis of α- and β-adrenoreceptor sensitivity and hence may have different cardiovascular responses to otherwise similar degrees of central activation (72). Similarly, the heart rate response to a mental arithmetic challenge may be associated with peripheral adrenoreceptor function (73).

Finally, persons developing hypertension may have altered vascular reactivity that is of peripheral origin, resulting in enhanced blood pressure responses to pharmacological challenges. One such challenge is caffeine, which potentiates the action of norepinephrine at the sympathetic nerve terminal and elevates peripheral vascular resistance. In studying blood pressure responses to caffeine, we saw progressively greater pressure rises in 185 subjects stratified into four risk groups, ranging from low-risk control subjects to medicated hypertensives (74). These subjects reported no differences in subjective activation or distress to the caffeine (75–77). In another study, caffeine given to patients with borderline hypertension induced a more prolonged increase in blood pressure over an hour of mental stress (78), again without differences in reported activation or distress (79). These studies suggest that the high-risk groups were experiencing caffeine and the stressors in the same way as the low-risk subjects. Caffeine raises blood pressure by actions at the blood vessel wall (77). The absence of self-reported differences between the groups and the known peripheral actions of caffeine strongly suggest that the pressure differences between hypertension risk groups were peripheral in origin.

In a similar vein, Folkow (6) argues that once structural remodeling of resistance vessels has begun and vascular wall thickening has begun to progress, blood pressure responses to any stimulus that raises pressure, be it of central or peripheral origin, will result in a disproportionate response because of the pressure flow dynamics of an increasingly restrictive vessel. In some studies, hypertensive subjects have been shown to exhibit greater blood pressure responses to a stressor than normotensive subjects in the absence of group differences in norepinephrine or epinephrine levels (80). Such evidence is again consistent with hypertensive subjects having a more reactive vascular system able to cause greater responses even when central influences are not altered. The lack of self-reported differences in arousal or affect in relation to the enhanced blood pressure rises in the studies reported above argue for the action of such peripheral factors, alone in the case of resting data or driven by activity originating in higher centers, during states of stress.

CONSIDERATIONS ABOUT EVIDENCE IN STUDIES OF REACTIVITY

Measurement of peripheral responses, such as blood pressure, may be useful in making group reactivity comparisons, but such evidence is limited with regard to underlying mechanisms. In turn, understanding how altered responses may contribute to specific diseases may be brought closer to reality by consideration of such mechanisms.

In the examples above, identification of cognitive-emotional factors may be facilitated by study designs combined with appropriately cautious interpretation of volunteers' self-reports. The study by Everson et al. (53), suggesting that hostile traits were responsible for exaggerated blood pressure responses, was based on selecting subjects using behavioral criteria and applying a specific hostility-provoking challenge on a sepa-

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rate day, thus enhancing reliability of the assessments. The high- and low-hostility groups were compared on a neutral challenge and found not to differ. Finally, their self-reports were congruent with the circumstances and their response differences. This allowed a degree of confidence in attributing the majority of the effect to cortical and limbic influences. This evidence is indirect nonetheless. More direct evidence will become available through the use of neuroimaging of different groups (81–84) during tonic and acute affective states.

The examples above suggest that study designs that include resting measurements, perhaps incorporating unstressed control days (21), along with careful assessment of self-reported activation and affect (52), may allow groups to be compared in terms of cardiovascular function in the absence of emotional influences. This presumably allows greater confidence in concluding that results may be due to influences other than cognitive and affective processes. The studies of responses to caffeine (74–79) or exposure to a novel laboratory in hypertension-prone men (61) relied on interpreting null differences in self-reports between the groups. Such null findings must be interpreted with caution. If measurement instruments are unreliable or poorly validated, concordances that might exist in the population will be obscured (77). Thus, a caveat is in order for conclusions based on such null relationships, and emphasis is placed on well-validated and reliable self-report measures used in consistent settings to reduce uncertainty. However, the extent to which emotional or subjective interpretations can be ruled in or out can aid in understanding results of given studies and in formulating comprehensive models based on reactivity.

Similar study design features may aid in separating central from peripheral sources of reactivity. However, this may prove difficult without additional application of specific autonomic function techniques not frequently used in behavioral studies. Discussions on these are provided in several sources (85). However, to the extent that these rely on null self reports, then similar caveats apply.

SUMMARY

Exaggerated physiological reactivity may begin at multiple levels of the nervous system and in disease-altered tissues. At the top level, cognitive-emotional responses may be sources of exaggerated reactivity. At the second level, physiological hyperreactivity may also result from hypothalamic or brainstem response tendencies that are not part of conscious awareness. At the lowest level, peripheral physiologic alterations may lead to hyperactivity, even in the presence of normal responses at more central levels. Establishing the connections between altered reactivity and disease incidence and virulence will depend on careful mechanistic work that goes beyond correlational studies. Recent models of early experience in rats may help us understand the origins of central nervous system alterations associated with emotional reactivity, stress responsiveness, and disease risk. We should not be deterred from consistent efforts to examine the systems basis for reactivity tendencies as well as the search for connections to the pathophysiology of cardiovascular disorders.

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