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ADRENOMEDULLARY, ADRENOCORTICAL, AND SYMPATHONEURAL RESPONSES TO STRESSORS: A META-ANALYSIS

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Abstract

Objective—Exposure to stressors alters activities of the adrenomedullary hormonal system (AHS), hypothalamic-pituitary-adrenocortical (HPA) axis, and sympathetic nervous system (SNS). Here we report results of a meta-analysis of the literature, examining inter-relationships among AHS, HPA, and SNS responses to stressors, as measured by plasma epinephrine (EPI), corticotrophin (ACTH), and norepinephrine (NE) levels.

Methods—The medical scientific literature was culled by PubMed searches, to retrieve publications describing original data about plasma EPI, ACTH, and NE levels measured before and during or after exposure to stressors. Magnitudes of responses were graded from a score of 0 for no response to 4 for a massive increase to ≥10 times the baseline value.

Results—A total of 15 stressors were identified for which at least 2 publications reported data for EPI, ACTH, and NE responses. A total of 60 reports were included. Mean EPI responses were strongly positively correlated with mean ACTH responses (r=0.93) and less strongly with NE responses (r=0.40). Plasma EPI responses were disproportionately larger than NE responses during hypoglycemia and smaller than NE responses during cold exposure without hypothermia, orthostasis, and active escape/avoidance. Plasma NE responses were disproportionately larger than ACTH responses during cold exposure without hypothermia and severe/exhausting exercise and smaller than ACTH responses during hypoglycemia.

Discussion—The results of this meta-analysis indicate a close association between adrenomedullary and hypothalamic-pituitary-adrenocortical responses across a variety of stressors. This association seems to be if anything stronger than that between adrenomedullary and sympathetic noradrenergic responses.

Keywords

Epinephrine; ACTH; Norepinephrine; Adrenomedullary; HPA; Sympathetic; Stress

It is by now well established that exposure to stressors alters activities of the adrenomedullary, adrenocortical, and sympathetic nervous systems. A sufficient number of

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studies have been published in which all three neuroendocrine systems have been monitored simultaneously to enable a meta-analysis of the literature, to examine inter-relationships among alterations in activities of these key effector systems upon exposure to different stressors and reassess long-standing concepts about these inter-relationships.

The first such concept is that there is a unitary “sympathoadrenal” system. In the early 20th century, the American physiologist, Walter B. Cannon, proposed that the sympathetic nervous system (SNS) and the adrenal gland hormone, “adrenin” (which came to be known as epinephrine [EPI] or adrenaline) function as a coordinated system maintaining homeostasis (a word he coined) during emergencies such as “fight or flight” situations (a phrase he introduced). According to Cannon’s concept, rapid activation of the sympathoadrenal system preserves the internal environment by producing compensatory and anticipatory adjustments that enhance the likelihood of survival. In 1939, Cannon formally proposed EPI as both the active principle of the adrenal gland and as the neurotransmitter of the sympathetic nervous system (Cannon and Lissak 1939), consistent with the functional unity of the sympathoadrenal system. The identity of the substance released at sympathetic nerve terminals remained controversial until 1946, when von Euler correctly identified norepinephrine (NE) as the sympathetic neurotransmitter in mammals (von Euler 1946).

A second, related concept is that there is a unitary stress response. Beginning in the 1930s, the East European physiologist, Hans Selye, popularized stress as a scientific idea (Selye 1936, 1956). Selye viewed all forms of stress as leading to (or being identical with) a stereotyped pathological pattern, including enlargement of the adrenal glands, shrinkage of the thymus gland (associated with atrophy of the lymph nodes and inhibition of inflammatory or immune responses), and ulcers or bleeding in the stomach or gastrointestinal tract. Selye defined stress as the nonspecific response of the body to any demand imposed upon it (Selye 1974). It was later demonstrated that these changes were associated with, and to at least some extent resulted from, activation of the hypothalamic-pituitary-adrenocortical (HPA) axis. Steroids released into the circulation from the adrenal cortex contribute to resistance but also be responsible for pathological changes. Selye’s concept that prolonged stress can produce physical disease and mental disorders is now widely accepted.

More than a half century elapsed before Selye’s doctrine of nonspecificity underwent experimental testing, which failed to confirm it (Pacak et al. 1998). Nevertheless, modern lay literature and medical websites continue to accept the notion of a unitary stress response. For instance, a Google search yielded about 14,900,000 hits for “the stress response.” According to Yahoo/Health, “The stress response is the set of physical and emotional changes the human body makes in response to a threat or stress. It sometimes is called the “fight-or-flight” response.” (As indicated above, it was Cannon who introduced this phrase.)

After adequately sensitive assay methods for plasma levels of NE and EPI became available, evidence rapidly accumulated for different noradrenergic vs. adrenergic responses in different situations (Cryer 1980; Robertson et al. 1979; Young et al. 1984). A new concept began to emerge, in which the SNS plays key roles in appropriate redistribution of blood flows in situations such as orthostasis, cold exposure, mild blood loss, locomotion, exercise,

altered salt intake, and water immersion; and the adrenomedullary hormonal system (AHS) responds to global or metabolic threats, such as hypoglycemia, hemorrhagic hypotension, exercise beyond an anaerobic threshold, asphyxiation, emotional distress, and shock. Evidence also accumulated for an association of SNS activation with active escape, avoidance, or attack and an association of AHS activation with passive, immobile fear.

More generally, according to a recently proposed concept, stress responses have a kind of "primitive specificity," and the AHS and SNS can respond differentially, depending on the type and intensity of the stressor as sensed by the organism and interpreted in light of experience (Goldstein 1995). Instead of the SNS becoming active only in emergencies, tonic sympathetic nervous outflow to several vascular beds, organs, and glands is present even under resting conditions, and everyday experiences such as orthostasis, locomotion, the post-prandial state, and exposure to altered environmental temperature can alter sympathoneural outflows, with little or no activation of the AHS. On the other hand, even a slight amount of glucoprivation, posing an overall metabolic challenge, evokes mainly an adrenomedullary response, without generalized SNS activation.

A third concept considered in this meta-analyses is that in response to situations that stimulate adrenomedullary secretion, there is concurrent activation of the HPA axis. The association of AHS with HPA activation might be even closer than that of AHS with SNS activation. Testing this concept requires analysis of experiments in which AHS, HPA, and SNS responses to various stressors are assessed simultaneously. This formal meta-analysis comprehensively assessed the clinical and preclinical literature in which plasma EPI, ACTH, and NE responses to stressors were measured in the same studies.

Methods

The medical scientific literature was culled by multiple computer searches of PubMed. The searches were designed to retrieve publications describing original data about plasma EPI, ACTH, and NE levels measured before and during or after exposure to stressors. The searches were followed by retrieving the reviewing printed research reports.

Magnitudes of responses were categorized according to the following criteria. If there was no significant change in the plasma levels of the dependent variable, a score of 0 was assigned. If there was a statistically significant increase, but less than a doubling, of the pre-stress baseline level, a score of 1 was assigned. If there was at least a doubling of the baseline value, up 3 times the baseline value, a score or 2 was assigned. If there were a large increase, from 3 up to 10 times the baseline value, a score of 3 was assigned. If there was a massive increase to ≥10 times the baseline value, a score of 4 was assigned.

For each stressor, the average across studies was used, without weighting studies by numbers of subjects.

As indicated in Table 1, a total of 15 different stressors were identified for which the available literature satisfied the above criteria.

Results

A total of 15 stressor categories and a total of 60 studies were included in the meta-analysis (Tables 1 and 2). The most frequently studied stressors were hypoglycemia and hemorrhagic hypotension. Although there was literature about other categories of stressor, such as cardiac arrest, pain, public performance, blood loss without hypotension, and mild exercise, the available literature did not meet the inclusion criteria for the meta-analysis.

Across the 15 stressors, mean plasma EPI responses (Table 2) ranged from 0.0 (cold exposure, no hypothermia) to 3.9 (hypoglycemia), ACTH responses ranged from 0.0 (cold exposure, no hypothermia) to 3.5 (exercise, severe/exhaustion), and NE responses ranged from 1.0 (hypoglycemia) to 3.5 (exercise, severe/exhaustion). Therefore, there was a substantial range of response intensities for all three dependent variables.

Mean EPI responses were strongly positively correlated with mean ACTH responses (Fig. 1) and less strongly with NE responses (Fig. 2). Plasma EPI responses were disproportionately larger than NE responses during hypoglycemia and smaller than NE responses during cold exposure without hypothermia, orthostasis, and active escape/avoidance. Plasma NE responses were disproportionately larger than expected for ACTH responses during cold exposure without hypothermia and severe/exhausting exercise and smaller than ACTH responses during hypoglycemia (Fig. 3).

Discussion

The results of this meta-analysis indicate a close association between adrenomedullary and hypothalamic-pituitary-adrenocortical responses across a variety of stressors. This association seems to be if anything stronger than that between adrenomedullary and sympathetic noradrenergic responses. The findings therefore favor the concept of a unitary adrenal system over that of a unitary sympathoadrenal system.

The analysis also supports the notion of “primitive specificity,” according to which stress responses occur in relatively specific neuroendocrine patterns. By promoting homeostasis, such patterning would have provided clear advantages in natural selection and therefore evolved. In contrast, Cannon’s and Selye’s theories, based as they are on the same stereotyped responses regardless of the stress, do not account adequately for outliers in the scatter plots relating EPI to NE and NE to ACTH responses. For instance, plasma EPI and ACTH responses to hypoglycemia are disproportionately larger than NE responses, and plasma NE responses to cold exposure without hypothermia are disproportionately larger than EPI or ACTH responses.

The largest AHS responses were reported for stressors that can be categorized in terms of posing a global or metabolic threat. There are several other stressors that should also pose this type of challenge to organismic integrity—pain, endotoxemia, and cardiogenic shock are examples; however, the studies culled on these topics did not fit the criteria for inclusion in the meta-analysis. Subcutaneous injection of formalin evokes relatively large adrenomedullary compared to sympathoneural responses in rats (Pacak et al. 1998). Administration of interleukin-1 elicits about a 5-fold increase in ACTH, 3-fold increase in

EPI, and 2-fold increase in plasma NE (Berkenbosch et al. 1989). Cardiac arrest results in massive increases in EPI levels and substantial increases in cortisol and NE levels (Foley et al. 1987), patients undergoing cardiopulmonary resuscitation have high EPI, ACTH, and NE levels (Lindner et al. 1996), and stress cardiopathy is associated with extraordinarily high plasma EPI and NE levels (Wittstein et al. 2005).

Meta-analysis of the available literature therefore supports a closer association of adrenomedullary with HPA than with SNS responses across a variety of stressors. There seems to be at least as good justification for the concept of coordinated adrenocortical-adrenomedullary responses as for coordinated adrenomedullary-sympathoneural responses.

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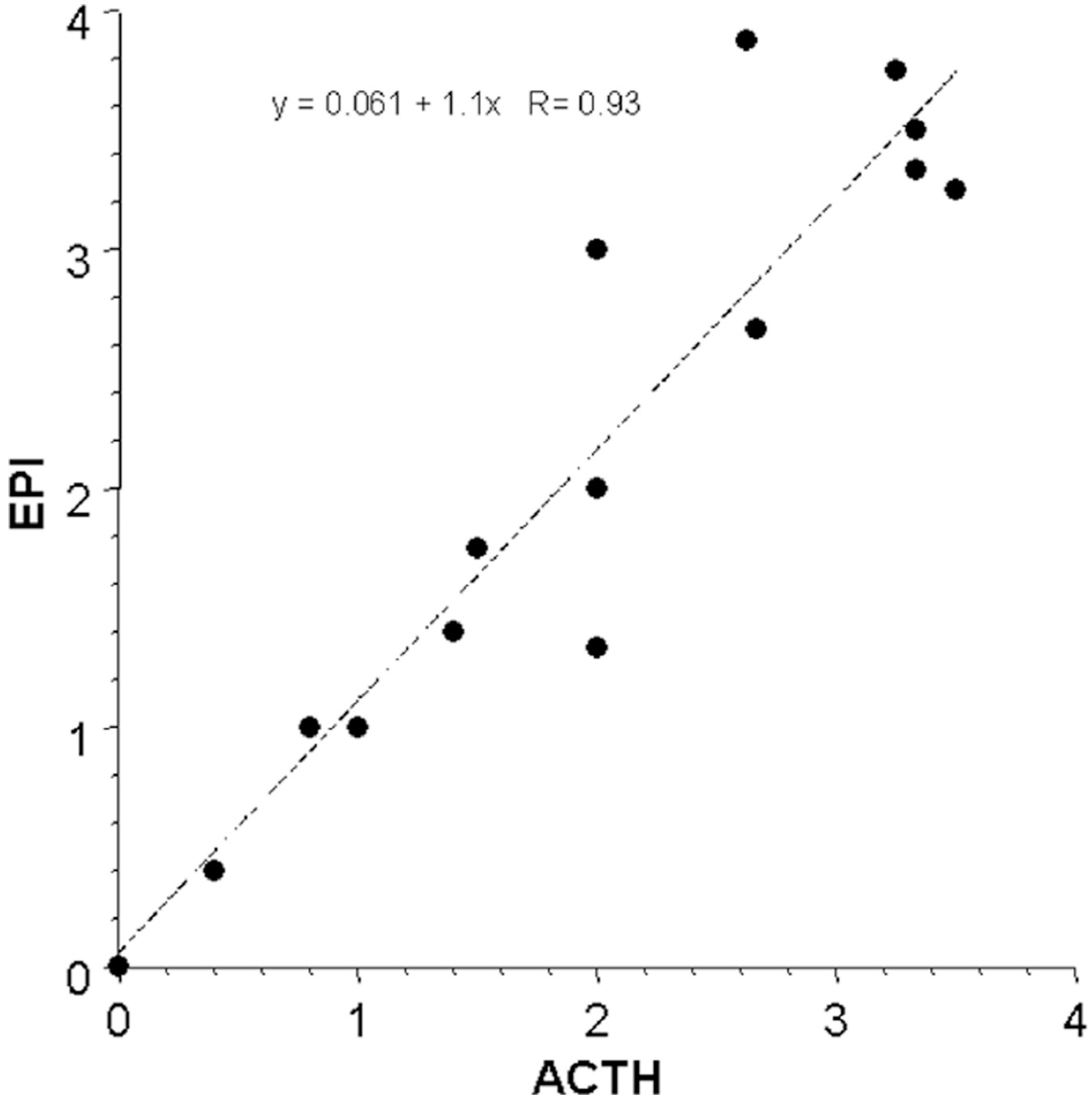

Fig 1.

Mean values for plasma levels of epinephrine (EPI) and corticotrophin (ACTH) across 15 different stressors. Equation is for the line of best fit.

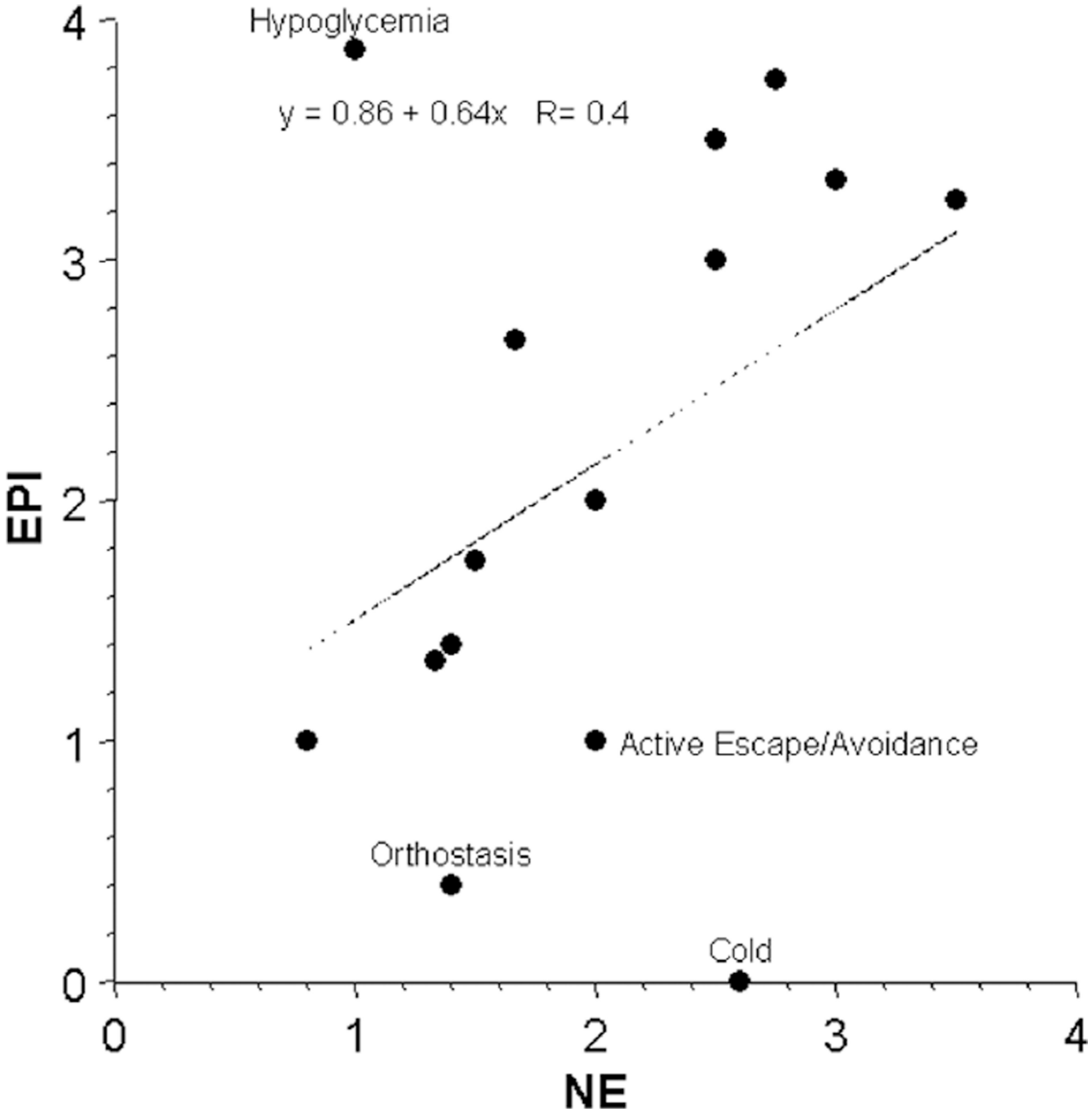

Fig 2.

Mean values for responses of plasma levels of epinephrine (EPI) and norepinephrine (NE) across 15 different stressors. Equation is for the line of best fit.

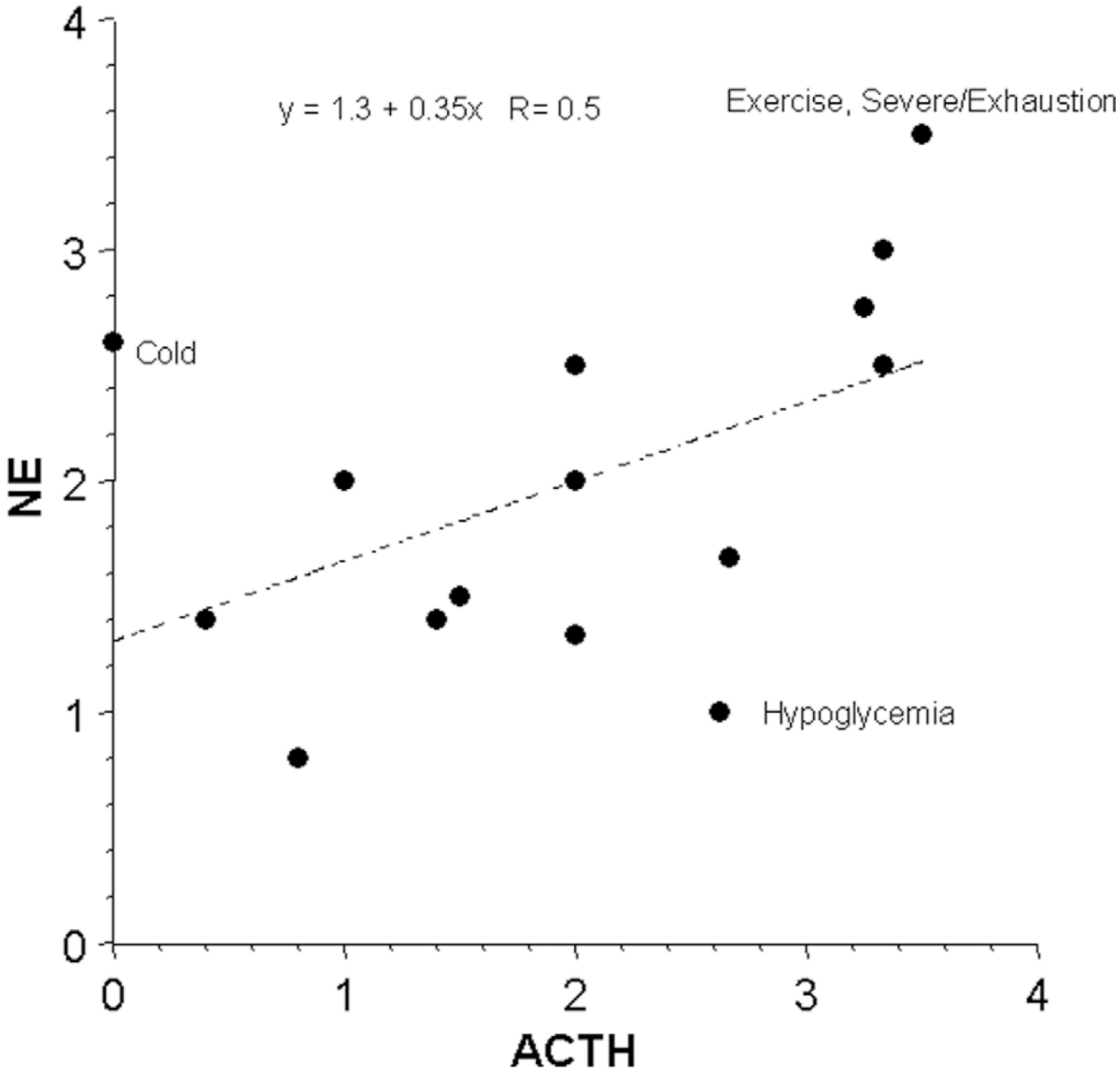

Fig 3.

Mean values for responses of plasma levels of norepinephrine (NE) and corticotrophin (ACTH) across 15 different stressors. Equation is for the line of best fit.

Table 1

Stressors in this review

Stressors are listed in approximate descending order of adrenomedullary activation (numbers in italics are numbers of studies for each stressor)

1	Hypoglycemia *8*
2	Immobilization (Rats) *4*
3	Hemorrhagic Hypotension *6*
4	Exercise, Severe or to Exhaustion *4*
5	Electroconvulsive Shock *3*
6	Social Stress in Rhesus Monkeys *2*
7	Fainting (Humans) *3*
8	Handling (Rats) *2*
9	Passive/Immobile/Conditioned Fear *4*
10	Surgery *5*
11	Mild Hypothermia *2*
12	Laboratory Mental Challenge (Humans) *5*
13	Active Escape/Avoidance (Rats) *2*
14	Orthostasis (Humans) *5*
15	Cold Exposure, No Hypothermia *5*

Table 2

Magnitudes of Responses to Stressors, from No Response (0) to Extremely Large Response (4) Values in boldface are means for each category.

Stressor	EPI	ACTH	NE	Reference	Notes
Hypoglycemia	4	2	1	Costa et al. 1993	Humans
Hypoglycemia	4	3	0	Giordano et al. 2003	Humans
Hypoglycemia	4	2	1	Mcgregor et al. 2002	Humans. [Cortisol]
Hypoglycemia	4	4	2	Pacak et al. 1998	Rats
Hypoglycemia	4	2	0	Radikova et al. 2003	Humans
Hypoglycemia	4	2	2	Schmid et al. 2007	Humans
Hypoglycemia	3	3	1	Toso et al. 1993	Dogs
Hypoglycemia	4	3	1	Watabe et al. 1987	Humans
Hypoglycemia	**3.9**	**2.6**	**1.0**		
Immobilization	4	4	3	Dronjak et al. 2004	Rats
Immobilization	4	3	3	Jezova et al. 1999	Rats
Immobilization	4	4	3	Pacak et al. 1998	Rats
Immobilization	3	2	2	Tjurmina et al. 2002	Rats
Immobilization	**3.8**	**3.3**	**2.8**		
Hemorrh. Hypotens.	4	3	3	Bereiter et al. 1986	Cats
Hemorrh. Hypotens.	4	3	2	Darlington et al. 1986	Rats
Hemorrh. Hypotens.	4	4	2	Grassler et al. 1990	Rats
Hemorrh. Hypotens.	4	3	3	Molina 2001	Rats
Hemorrh. Hypotens.	1	4	1	Pacak et al. 1998	Rats
Hemorrh. Hypotens.	4	3	4	Wade et al. 1991	Swine
Hemorrh. Hypotens.	**3.5**	**3.3**	**2.5**		
Exercise, Severe	4	4	4	Deuster et al. 1989	Humans
Exercise, Severe	4	4	4	Nagata et al. 1999	Horses
Exercise, Severe	3	3	3	Oleshansky et al. 1990	Humans
Exercise, Severe	2	3	3	Schwarz & Kindermann 1990	Humans
Exercise, Severe	**3.3**	**3.5**	**3.5**		
Electric shock	3	3	3	de Boer et al. 1990	Rats. [Corticosterone]
Electric shock	3	4	3	Thiagarajan et al. 1989	Rats

Stressor	EPI	ACTH	NE	Reference	Notes
Electric shock	4	3	3	Weinger et al. 1991	Humans
Electric shock	**3.3**	**3.3**	**3.0**		
Social Stress	4	3	3	Ayala et al. 2004	Monkeys
Social Stress	2	1	2	Habib et al. 2000	Monkeys
Social Stress	**3.0**	**2.0**	**2.5**		
Fainting	2	2	0	Carroll et al. 1995	Humans
Fainting	3	3	3	Gasiorowska et al. 2005	Humans
Fainting	3	3	2	Jardine et al. 1997	Humans
Fainting	**2.7**	**2.7**	**1.7**		
Handling	2	2	2	Dobrakovova et al. 1993	Rats
Handling	2	1	1	Makatsori et al. 2005	Rats
Handling	2.0	1.5	1.5		
Fear	3	2	3	Korte et al. 1992	Rats
Fear	3	3	3	Nijsen et al. 2000	Rats
Fear	0	1	0	Pitman et al. 1992	Rats
Fear	1	0	0	Pitman et al. 1995	Rats
Fear	**1.8**	**1.5**	**1.5**		
Surgery	0	0	0	Chi et al. 2001	Humans. Neurosurg.
Surgery	3	3	2	Donald et al. 1993	Humans
Surgery	1	1	2	Kudoh et al. 1999	Humans
Surgery	2	2	1	Nguyen et al. 2002	Humans
Surgery	1	1	2	Udelsman et al. 1987	Humans
Surgery	**1.4**	**1.4**	**1.4**		
Mild Hypothermia	2	2	2	Frank et al. 1995	Humans. Post-op.
Mild Hypothermia	0	2	0	Chi et al. 2001	Humans. Neurosurg.
Mild Hypothermia	**1.0**	**2.0**	**1.0**		
Lab. Mental Challenge	0	0	0	Costa et al. 1993	Humans
Lab. Mental Challenge	0	0	0	Gerra et al. 2000	Humans
Lab. Mental Challenge	2	1	2	Gerra et al. 2001	Humans
Lab. Mental Challenge	1	2	1	Schommer et al. 2003	Humans
Lab. Mental Challenge	2	1	1	Yoshiuchi et al. 1997	Humans

Stressor	EPI	ACTH	NE	Reference	Notes
Lab. Mental Challenge	**1.0**	**0.8**	**0.8**		
Active Escape/Avoidance	1	2	2	de Boer et al. 1990	Rats
Active Escape/Avoidance	1	0	2	Korte et al. 1992	Rats
Active Escape/Avoidance	**1.0**	**1.0**	**2.0**		
Orthostasis	0	0	2	Carroll et al. 1995	Humans
Orthostasis	1	0	1	Gasiorowska et al. 2005	Humans. LBNP
Orthostasis	0	0	1	Jardine et al. 1997	Humans
Orthostasis	0	0	1	Mlynarik et al. 2007	Humans
Orthostasis	1	2	2	Radikova et al. 2003	Humans
Orthostasis	**0.4**	**0.4**	**1.4**		
Cold, No Hypotherm.	0	0	3	Fukuhara et al. 1996	Rats
Cold, No Hypotherm.	0	0	3	Leppaluoto et al. 2008	Humans
Cold, No Hypotherm.	0	0	2	Marino et al. 1998	Humans. [Cortisol]
Cold, No Hypotherm.	0	0	3	Pacak et al. 1998	Rats
Cold, No Hypotherm.	0	0	2	Wittert et al. 1992	Humans
Cold, No Hypotherm.	**0.0**	**0.0**	**2.6**		

Abbreviations: AHS=adrenomedullary hormonal system; HPA=hypothalamic-pituitary-adrenocortical system; SNS=sympathetic noradrenergic system; LBNP=lower body negative pressure; ACTH=corticotrophin