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Fearful Behavior, Body Size, and Serum IGF-I Levels in Nervous and Normal Pointer Dogs

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UHDE, T. W., L. C. MALLOY AND S. O. SLATE. *Fearful behavior, body size, and serum IGF-I levels in nervous and normal pointer dogs.* PHARMACOL BIOCHEM BEHAV 43(1) 263-269, 1992.—Panic disorder in adult humans is associated with disturbances in hypothalamic-growth hormone (GH) function and children with emotional deprivation or severe anxiety develop growth retardation. Nervous pointer dogs, a genetic animal model of panic disorder or severe anxiety, are characterized by extreme fearfulness and avoidance of novel stimuli. This experiment investigated indices of body stature, weight, and insulin-like growth factor I (IGF-I) levels in a colony of purebred nervous and purebred normal pointer dogs. The genetic line of nervous dogs had significantly greater scores of fearfulness, lower total body weights, lower weight/height ratio, and lower serum IGF-I levels than the normal line of pointer dogs. There was an inverse relationship between degree of fearfulness and total body weight in female, but not male, dogs. Stepwise logistic regression analysis indicated that the severity of fear behaviors, height, and weight were significantly associated with IGF-I levels. The best predictor of IGF-I levels in the dogs, however, was the severity of fearful behaviors elicited by exposure to novel stimuli and humans. These observations suggest that the neurobiological substrates of alarm, arousal, and fear influence hypothalamic-GH-somatomedin-mediated effects on weight and, to a lesser extent, height. Findings are discussed in terms of their relevance to future research in humans with anxiety disorders.

Animal behavior Anxiety disorders Body size Body weight Dogs Gender differences Growth Insulin-like growth factor-I/somatomedin C

RECENT evidence from our laboratory suggests a widespread decrement in growth hormone (GH) function in panic disorder patients as manifested by blunted growth hormone responses to single-dose challenges of clonidine (37,39,42). GH-releasing hormone (GHRH) (41), yohimbine, and caffeine (41). Panic disorder patients also tend to have a decreased response to the delayed rise in GH after glucose challenge (41). Moreover, unlike reports in major depression [for review, see (12)], panic disorder is not characterized by paradoxical rises in GH after thyrotropin-releasing hormone (TRH) stimulation (36).

Although the mechanism underlying the blunted GH response to clonidine in neuropsychiatric syndromes has largely been attributed to downregulated α_2-adrenergic receptors in the hypothalamus (2,22,32,42), a number of different mechanisms, both external and intrinsic to the hypothalamic-GH axis, might explain these observations (41). It now appears unlikely that a single abnormality in α_2-adrenergic receptor function can explain the global pattern of downregulated GH function in panic disorder patients. We have also noted that some children with anxiety disorders, in otherwise good physical health, may have unusually small statures (40,41). Taken together, these observations suggest that alterations in GH function may have an impact on the rate and pattern of growth in humans with panic disorder.

Nervous pointer dogs have been suggested as an animal model of human anxiety [(4,11,14,15,17,45); for review, see (23)]. Dogs with short stature, which has been associated with blunted GH responses to clonidine (7), also have been reported to respond favorably to treatment with bovine or human GH. Dogs with so-called "GH-responsive short stature" may have a high rate of nervous behaviors (Lorthrop, personal communication), although systematic studies are required to document this clinical impression. Dwarf German shepherds also have been reported to have decreased levels of somatomedin/insulin-like growth factor I (IGF-I) (7,18). Another line of evidence suggests that dogs with licking compulsions, leading to forepaw alopecia, respond to clomipramine (9) and, possibly, GH supplementation (Lothrop, personal

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communication). Nervous pointer dogs, like panic disorder humans (20,26), may have increased rates of compulsive behaviors including licking, biting, and pulling various body parts (e.g., lips, hair). Taken together, these observations, in both humans and animals, suggest that decreased GH function may be connected to a repertoire of nervous behaviors and short stature.

In this study, we investigated body size, weight, and serum somatomedin C/IGF-I levels in nervous and normal pointer dogs. Our findings of significantly decreased weight and lower IGF-I levels in nervous dogs, together with other lines of evidence, suggest that the presence of an anxiety disorder or exposure to major stressors, if present at a critical stage of development, may represent an independent risk factor for disturbances in growth velocity, body size, and weight.

METHOD

Dog Colony

The NIH Section of Anxiety and Affective Disorders maintains a colony of purebred nervous and purebred normal pointer dogs. The nervous line of dogs in our colony are 9- to 11-generation offspring of the original Arkansas pointer dog model of human anthromorphobia (5). Although the nervous and normal lines each descend from a single pair of purebred pointers, the normal dogs have been selectively outbred during the past 25 years to sustain fertility. There never has been selective breeding or maintenance of the colony on the basis of gender, weight, height, or other body dimensions. Breeders have been selected for the most fearful behaviors in the nervous line and for the least fearful behaviors in the normal line.

The colony includes 13 female and 7 male nervous dogs and 10 female and 12 male normal dogs ($\chi^2 = 1.62$, $p = 0.20$). Although the average age of the colony is advanced (7.26 ± 1.49 years), there have been no differences in mortality in relation to the line or gender of dogs in our current colony.

Dogs are housed in pairs in kennels 31.5 ft^2 containing both indoor and outdoor runs. Dogs are separated by gender but not according to diagnostic group (i.e., both nervous and normal dogs may share a kennel). All dogs had unlimited lifetime access to food. Dogs with clinical or laboratory evidence of neuroendocrine, cardiovascular, gastrointestinal, or metabolic diseases were excluded from this study ($n = 2$). Dogs with changing body weights ($n = 3$) over the preceding 6-month period evidence were excluded from the study. Data were collected on all remaining dogs ($n = 37$). With the exception of single-dose caffeine or clonidine challenges, all animals had been drug free for a minimum of 6 months.

Measurement of Body Size and Weight

Sixteen nervous (10 female and 6 male) and 21 normal (10 female and 11 male) dogs, $\chi^2(1) = 0.810$, p = NS, with an average age of 7.40 ± 1.07 and 7.16 ± 1.76, $t(35) = -0.486$, p = NS, were evaluated for adult stature and weight.

Height in centimeters was determined by measuring the distance between the bottom of the foot (i.e., floor) and the top of the shoulder while the animal was standing erect in a natural position. Length (cm) was assessed at the same time under identical conditions and was determined by measuring the distance from the tip of the nose to the base of the tail.

Weight (kg) represented the mean of two to four consecutive measurements obtained while the animal was standing on a standard Ken Kage (Wheeling, IL) electronic scale. Weights were recorded between 9:00–10:00 a.m. The ratio of weight (kg)/height (cm) was calculated in each dog.

Behavioral Ratings

The following ratings of fearful behavior were obtained: human interaction test (HIT) score, new morbidity index (NMI), and the global rating scale (GRS). All the scales rate a range of nervous behaviors (e.g., retreat, urination, defecation, tucked tail position, salivation, freeze response, circling, and tremor) under different conditions.

The HIT (range −24 to +24) score is obtained while the dog is in its home cage. On this scale, negative (−) ratings represent more fearful behavior whereas positive (+) ratings represent various degrees of *increasingly* normal behavior.

The NMI is derived from the assessment of fearful behaviors and motor activity under four separate conditions: while the dog is alone in a research chamber (DA), during exposure to a passive human (PH), while the dog is being called by a human (HC), and while the dog is being approached by a human (HA). The NMI has been used extensively in the study of dog behavior (16,21) and provides an integrated measure of fearfulness. The possible scores on the NMI range from 3–15, with low scores representing the most normal behavior.

A global rating of nervousness (range 1–9) was obtained during the same aforementioned experimental conditions (DA, PH, HC, and HA). Ratings of 1 represent totally normal dog behavior whereas a score of 9 indicates severely abnormal, bizarre, or fearful behavior. The average of the global ratings

TABLE 1

RATINGS OF FEARFULNESS IN NERVOUS AND NORMAL POINTER DOGS

Rating Scales	Control Dogs	Nervous Dogs	ANOVA
Human interaction test	8.52 ± 8.09	−4.31 ± 3.55	D, $F(1, 33) = 30.55, p < 0.00$; G, $F(1, 33) = 1.07, p$ = NS; D × G, $F(1, 33) = 0.25, p$ = NS
New morbidity index	7.62 ± 3.32	12.38 ± 2.42	D, $F(1, 33) = 20, p < 0.00$; G, $F(1, 33) = 2.6, p$ = NS; D × G, $F(1, 33) = 0.77, p$ = NS
Global rating scale	4.25 ± 2.34	8.17 ± 0.67	D, $F(1, 33) = 37.67, p < 0.00$; G, $F(1, 33) = 1.65, p$ = NS; D × G, $F(1, 33) = 0.04, p$ = NS

under the four testing conditions was used to provide a mean global rating for each dog. Thus, the mean global score of each animal reflects an overall assessment of the dogs' behaviors under all four testing conditions. This scale also has been discussed in greater detail elsewhere (16).

All the behavior rating scales were administered at the same time within 3 weeks of body weight and height determinations.

IGF-I Levels

IGF-I was measured using the Nichols (Nichols Institute, San Juan Capistrano, CA) radioimmunoassay (RIA) technique (43). Blood samples for determination of IGF-I levels were obtained after a single blood drawing. Intra- and interassay coefficients of variations were both 17%.

Statistics

Two-factor [genetic line (i.e., nervous vs. normal) and gender] analysis of variance (ANOVA) or Mann-Whitney *U*-tests were employed to assess differences between the nervous and normal pointer dogs in terms of height (H), length (L), weight (W), W/H ratio, serum IGF-I levels, and ratings of fearful behavior. Posthoc testing was performed by Bonferroni's *t*-test.

Stepwise (forward) logistic regression analysis was performed using the SYSTAT (1990) program to identify factors associated with IGF-I levels. The criteria to enter or remove a variable, respectively, from the model was set at $p < 0.05$ and $p > 0.15$. The variables considered for each of the three stepwise analyses are presented in the Results section. Relationships among ratings of fearful behavior, dimensions of body size or weight, and IGF-I levels were assessed by Pearson product-moment or partial correlation coefficients.

Data are reported as mean ± SD. All *p* values greater than or equal to 0.10 are reported as NS. Differences in degrees of freedom reflect missing data.

RESULTS

Behavioral Ratings

As indicated in Table 1, dogs from the nervous genetic line had ratings indicative of significantly greater fearfulness compared to the normal genetic line of dogs. There were no diagnosis (D) (i.e., nervous vs. normal) × gender (G) or main gender effects; however, if we dichotomize our colony into dogs above or below 11 on the NMS index we find that approximately 75% of dogs with scores >11 (indicative of severe fearfulness) are female.

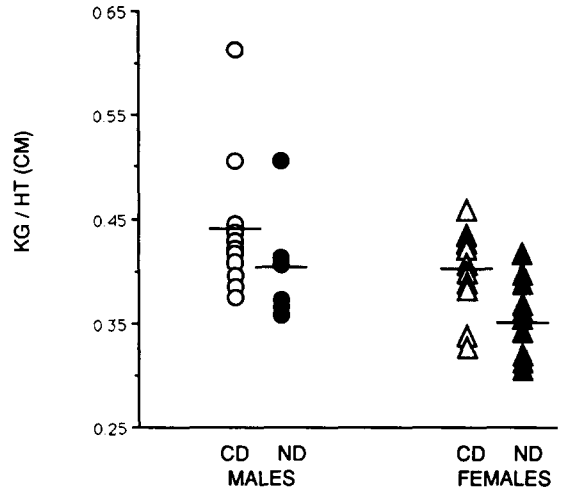

FIG. 2. Although male dogs (circles) had higher weight-to-height ratios than female dogs (triangles), there was a main effect of diagnosis ($p < 0.009$) as reflected by a significantly reduced weight/height ratio in nervous dogs (ND; shaded symbols) compared to control dogs (CD; open symbols).

Body Size

There was a significant main effect of D, $F(1, 33) = 7.530$, $p < 0.01$, and G, $F(1, 33) = 15.117$, $p < 0.000$, on weight, but no D × G, $F(1, 33) = 0.003$, p = NS, interaction. The nervous female dogs, therefore, were consistently the smallest group in terms of weight (mean = 19.5 ± 2.9 kg) compared to the normal male (mean = 26.6 ± 2.9 kg, Mann-Whitney *U*-test = 110.00, $p = 0.000$), nervous male (mean = 22.0

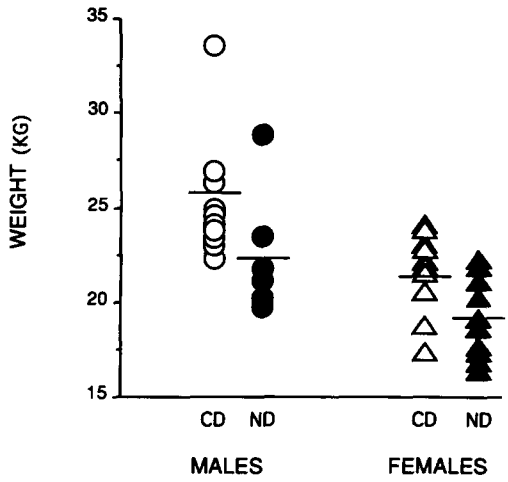

FIG. 1. Female dogs (triangles) had significantly lower total body weights than male (circles) dogs. Nervous dogs (ND; shaded symbols), independent of gender, however, had significantly lower weight compared to control dogs (CD; open symbols).

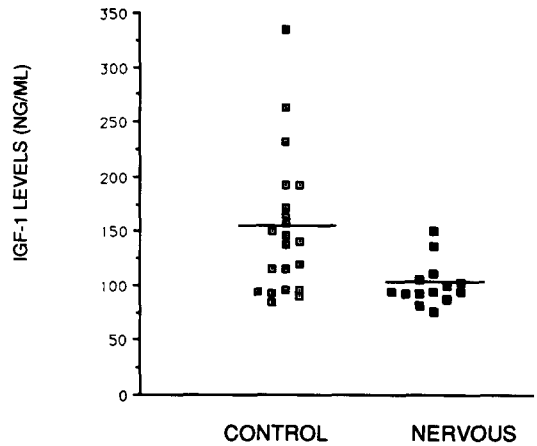

FIG. 3. The mean serum IGF-I levels in nervous dogs (101.36 ± 20.08 ng/ml SD) were significantly lower than control dogs (151.67 ± 63.86 ng/ml) ($p < 0.008$). There was no significant main effect of gender or diagnosis × gender interaction.

TABLE 2

VARIABLES CONSIDERED IN STEPWISE LOGISTIC REGRESSION ANALYSES

Categorical variables
Diagnosis (i.e., nervous or normal line)
Gender
Continuous variables
Height
Length
Weight
Weight/height ratio
Months of age
Global score
HIT score
NMI score

± 2.3 kg, Mann-Whitney U-test = 49.00, p = 0.039) and normal female (mean = 23.0 ± 3.172 kg, Mann-Whitney U-test = 105.00, p = 0.013) dogs (Fig. 1). In terms of the weight/height ratio (Fig. 2), there was a similar significant main effect of D, $F(1, 33) = 7.776$, $p < 0.009$, and G, $F(1, 33) = 54.585$, $p < 0.000$, but no significant D × G interaction, $F(1, 33) = 0.106$, p = NS.

In terms of height (H) and length (L), there was a significant main effect of G [H, $F(1, 35) = 11.288$, $p < 0.002$; L, $F(1, 35) = 5.833$, $p < 0.021$] but no significant main effect of D [H, $F(1, 35) = 2.301$, p = NS; L, $F(1, 35) = 0.838$, p = NS] or D × G interaction [H, $F(1, 33) = 0.255$, p = NS; L, $F(1, 33) = 0.072$, p = NS].

IGF-I Levels

As indicated in Fig. 3, the serum levels of IGF-I were significantly lower in nervous (mean = 101.36 ± 20.08 SD) compared to the normal (mean = 151.67 ± 63.86 SD) [D, $F(1, 31) = 8.114$, $p < 0.008$] dogs. There was no significant main effect of G, $F(1, 31) = 2.721$, p = NS, or D × G, $F(1, 31) = 2.163$, p = NS, interaction.

The stepwise logistic regression analysis was performed to identify variables associated with IGF-I levels. Variables that were entered into the stepwise logistic regression are presented in Table 2. The regression analysis indicated that the severity of fearful behaviors (i.e., scores on the global rating scale), height, and weight were the only variables significantly associated with IGF-I levels (Table 3). The best predictor of IGF-I levels, however, was severity of anxiety, that is, dogs with the most fearful behaviors on the global rating scale had the lowest levels of IGF-I ($r = -0.66$, $p < 0.000$) (Fig. 4).

Behavioral Ratings: Relationship with Body Size and Weight

For the total group of dogs, dogs with the most fearful behaviors on the global ($r = -0.43$, $p < 0.007$) (Fig. 5),

TABLE 3

VARIABLES ASSOCIATED WITH IGF-I LEVELS

Step	Variable	r	R^2	p
1	Global	0.662	0.439	0.000
2	Height	0.571	0.622	0.000
3	Weight	−0.424	0.690	0.014

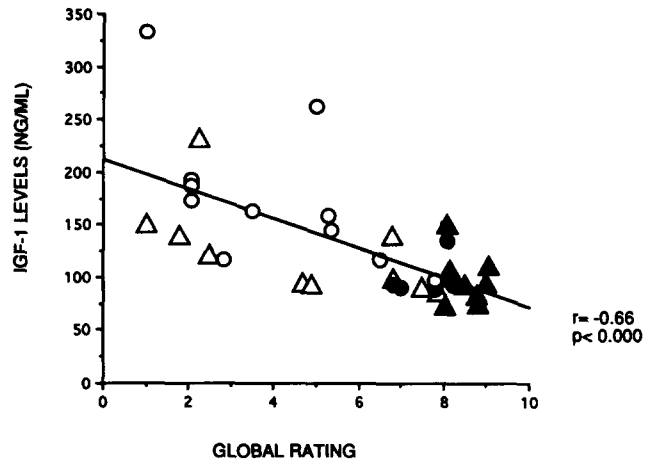

FIG. 4. There was a significant negative correlation between serum IGF-I levels and global ratings of fearfulness ($r = 0.66$, $p < 0.000$) for the total group of nervous (shaded symbols) and control (open symbols) dogs. The global rating scale has a range of 1-9, with 9 representing the most severe degree of fear behaviors. Male and female dogs are depicted by circles and triangles, respectively.

NMI ($r = 0.52$, $p < 0.001$), and HIT ($r = 0.46$, $p < 0.003$) scales had the lowest body weights. As illustrated in Fig. 6, these findings were most evident in female dogs, particularly those from the nervous genetic line.

DISCUSSION

Recent observations in children with severe anxiety disorders indicate that they may have alterations in size and growth velocity (40,41) and adult panic disorder patients have disturbances in hypothalamic-GH axis function (2,22,39,41,42). Nervous pointer dogs are an animal model for human anxiety disorders, including panic disorder [for review, see (45)], and dogs with nervous behaviors have been reported to respond to treatment with GH. For these reasons, we investigated the

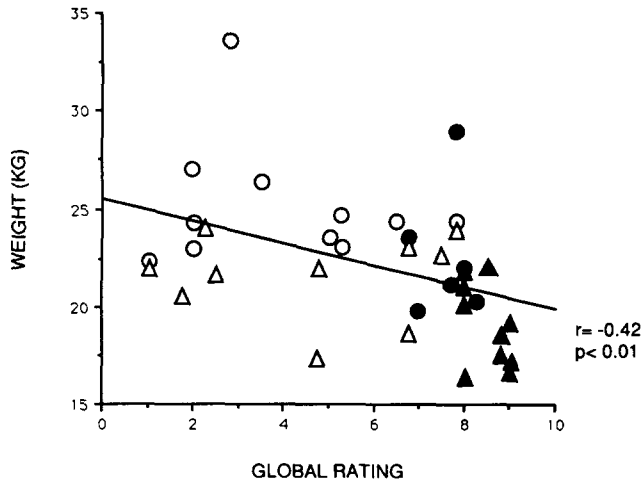

FIG. 5. Body weight (kg) was negatively correlated with ratings of fearfulness ($r = -0.42$, $p < 0.01$). Nervous (shaded symbols) and control (open symbols) dogs with the most severe ratings of fearfulness had the lowest body weights.

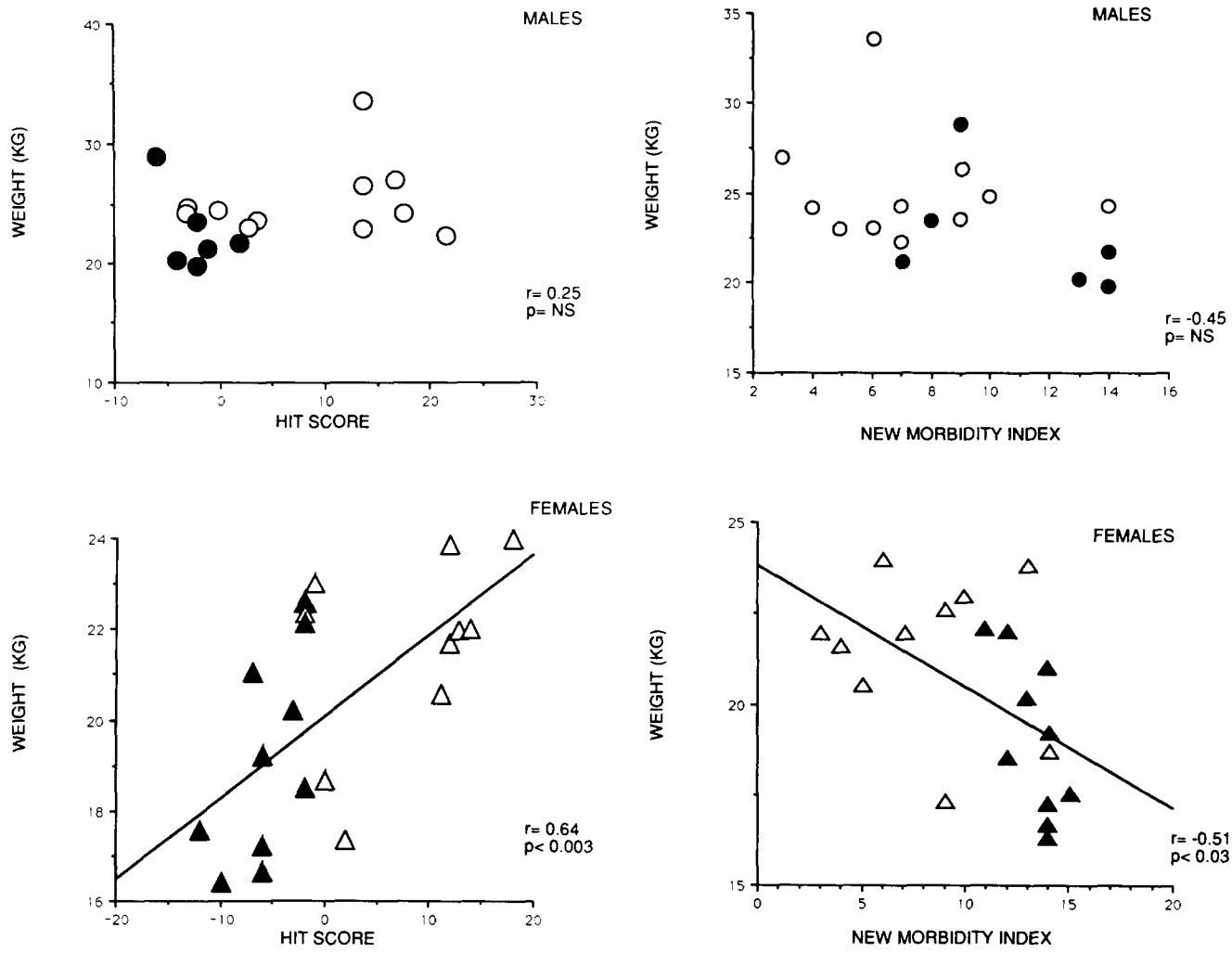

FIG. 6. There was a significant inverse relationship between severity of fear behaviors on two separate rating scales and total body weight in female, but not male, dogs. Lower (i.e., negative) and higher scores on the HIT (range −24 to +24) and new morbidity index (range 3–15), respectively, represent the most severe degrees of fearfulness. Nervous dogs are depicted in shaded symbols.

size, weight, and IGF-I levels of adult nervous and normal pointer dogs.

The results of our study indicate that dogs from the nervous genetic line have significantly reduced weights compared to dogs from the normal line. Although we found no interactive effects between genetic line and gender on weight by ANOVA, female, but not male dogs, with the most severe fearful behaviors weighed the least. Moreover, within our entire colony of dogs 75% of dogs with the most pathologic behaviors, independent of genetic line, were female. In fact, genetic-behavioral dissociations (i.e., when the behavior is opposite that predicted by the genetic line of the parents) tend to be, when present, based upon genetically normal females exhibiting abnormal fearful behaviors and genetically fearful males demonstrating normal behaviors. These findings are interesting in relation to the two- to threefold greater rate of panic disorder that has been observed in women compared to men (8,27). These observations raise the question as to whether panic disorder (and its homologous syndrome in dogs) is more common in females, as is widely accepted, or whether the syndrome, when present, is typically more severe in females. Within this latter context, it is interesting that women compared to men with panic disorder tend to develop more severe avoidance behaviors [(34); for review, see (38)]. It is possible, therefore, that the presence of a particular illness state (e.g., anxiety disorder) may have different consequences in females compared to males.

While we failed to find robust decreases in height in adult nervous dogs, nervous dogs had nonsignificant decreases in height compared to normal dogs. It is possible that nervous pointer dogs might have altered growth velocity or decreased stature at different (i.e., younger) stages of growth development yet achieve normal adult height. In fact, children with psychosocial short stature (24,25) often achieve normal adult sizes despite prior marked disturbances in growth velocity and/or stature. Future studies in this dog model will explore whether exposure to stressors at different stages of development will produce differential abnormalities in growth velocity, body size, or weight in the nervous compared to normal line of pointer dogs.

One of the most interesting findings was the significantly reduced levels of IGF-I in nervous vs. normal dogs. Both GH

and IGF-I influence body weight and height (3,13, 28,29,31,35) but, depending upon the animal model, each of these neuropeptides may have differential effects on skeletal growth and total body weight. Miniature poodles have lower levels of IGF-I than standard poodles (10) and larger breeds of dogs tend to have higher IGF-I levels than smaller breeds (6). In the mutant dwarf rat, GH and IGF-I produce similar increases in weight but GH stimulates significantly greater increases in bone growth than IGF-I (33,44). Given this apparent differential effect of GH and IGF-I on target sites of action (33) and apparent differences in weight vs. height between our two lines, further studies are needed to determine whether differences in basal or stimulated canine GH secretion, as well as IGF-I, exist between nervous and normal dogs. Although it would have been desirable to measure GH levels in the current study, we have been unable so far to develop a reliable RIA assay technique for canine GH.

We found a significant inverse relationship between severity of fearfulness and both body weight and IGF-I levels. Moreover, in a logistic regression analysis we found fear behaviors to be the best predictor of IGF-I levels. Taken together, these observations suggest that the neurobiological substrates of alarm, arousal, and fear may influence hypothalamic-GH-somatomedin function. Within this context, recent attempts to develop a series of GH stimulation paradigms for the diagnosis of idiopathic short stature in humans (1,19) may need to take into account the presence of pathologic anxiety states to improve diagnostic specificity.

There are a number of factors, other than GH or IGF-I dysregulation, that might explain the apparent decrements in weight, weight-to-height ratio, and, to a lesser extent, height in nervous dogs. These include poor nutrition or markedly abnormal caloric intake (i.e., starvation), malabsorption, thyroid or liver disease, or renal failure. All dogs with medical diseases were excluded from our study and no association between thyroid dysfunction and abnormal behaviors has been uncovered in several independent evaluations of our colony. All dogs from both lines had free access to unlimited food and water throughout their lives. Therefore, it is unlikely that any of the aforementioned variables directly contributed to alterations in weight or size. Nonetheless, these variables, primarily nutritional status, should be assessed and controlled for in a more precise manner in future studies. It is possible that chronic severe distress (i.e., fearfulness) in selective panic disorder humans and nervous pointer dogs may lead to decreased appetite, reduced caloric intake, and secondary disturbances in hypothalamic-GH function. Conversely, it is also plausible, because insulin stimulates food consumption in hypophysectomized rats (30), that reduced levels of IGF-I in nervous dogs is a "primary" disturbance that leads to reduced caloric intake and lower body weights.

To the extent that nervous pointer dogs represent a valid model of pathologic anxiety, our preliminary findings suggest that three areas should be explored in humans. First, longitudinal studies should investigate whether disturbances in growth velocity and stature or weight are significantly more common in children with anxiety disorders than children without anxiety disorders. Second, it will be important to determine whether prepubescent girls, compared to boys, with panic disorder are particularly vulnerable to disturbances in growth velocity. Third, future research should simultaneously assess the status of the hypothalamic-GH-somatomedin axis and several neurotransmitter systems implicated in the neurobiology of anxiety (e.g., noradrenergic, serotonergic, adenosinergic, and GABAergic systems) at different ages and phases of illness in humans with anxiety disorders.

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