# NEURAL
# and
# METABOLIC
# CONTROL
# of
# MACRONUTRIENT
# INTAKE

Edited by
Hans-Rudolf Berthoud, Ph.D.
Randy J. Seeley, Ph.D.

# 3  Is There a Specific Appetite for Protein?

*Bennett G. Galef, Jr.*

## CONTENTS

## 1   THE WISDOM OF THE BODY

The title Walter Cannon[1] devised for his classic monograph *The Wisdom of the Body* characterized accurately the extraordinary efficacy of physiological systems in maintaining homeostatic equilibria. As Cannon[1] demonstrated in successive chapters, the body possesses internal processes that detect deviations from optimal values in the blood content of water, salt, sugar, protein, fat, calcium, and oxygen, as well as internal effectors capable of redressing any detected imbalance.

Cannon was aware of the important role of behavioral interactions with the external world in maintaining the internal milieu, and devoted an early chapter of *The Wisdom of the Body* to discussion of hunger and thirst as appetites assuring ingestion of substances needed to maintain homeostasis.

## 2   BEHAVIORAL HOMEOSTASIS

Current appreciation of the role of behavior in maintenance of internal homeostasis rests, however, not on the work of Cannon, but on that of Curt Richter.[2-4] It was Richter who forcefully extended the concept of homeostasis from internal physiological processes to exteroceptors and to behaviors

involved in the identification, acquisition, and ingestion of nutrients needed to maintain or restore the internal milieu.

In a series of classic studies carried out during the 1930s and 1940s, Richter demonstrated that, when challenged either by artificially induced nutrient deficiencies or by homeostatic perturbations resulting from spontaneous changes in physiological state, rats would alter their patterns of food selection so as to redress any disturbance to internal homeostasis that they experienced.

The results of Richter's empirical work led him to conclude that animals (and humans) could select foods to ingest that would remedy any deficiency that they experienced in their internal reserves of each micro- and macronutrient.[2] Thus, by implication, Richter came to champion the view that animals and humans possessed: (1) interoceptors able to identify deficiencies in each of the 30 to 50 nutrients they required for health, (2) exteroceptors able to identify each of these nutrients in the external world, and (3) specific appetites that would cause them to seek out and ingest appropriate substances when interoceptors detected deficiency states.

## 3    SODIUM APPETITE

Richter's[2] model of "total self-regulatory functions" was, in essence, an extrapolation from his understanding of the regulation of sodium.[3] In 1936, Richter[4] had found that adrenelectomized rats, that die from sodium loss in a few days if fed only water and a standard rodent diet, will survive indefinitely if also given access to concentrated sodium solutions that intact rats find so unpalatable that they refuse to ingest them. Richter suggested that ingestion by adrenalectomized rats of concentrated sodium solutions was the result of innate systems detecting sodium deficiency, identifying sources of sodium in the external world, and motivating ingestion of sodium.

### 3.1    BEHAVIORAL EVIDENCE

Subsequent experiments have shown that Richter was essentially correct in his conclusion that there are motivational systems in rodents, and in mammals more generally, that enable them to detect sodium depletion and respond to such depletion behaviorally, thus restoring homeostatic equilibrium.[5,6] Further, there is evidence consistent with the view that such adaptive responses of rodents to sodium depletion are unlearned: (1) rats show enhanced ingestion of sodium salts the very first time that they are made sodium deficient,[7] and they do so within seconds of their first contact with sodium-salt solutions;[8,9] (2) sodium-deficient rats avidly and immediately ingest LiCl[10,11] that tastes like NaCl[12] but does not alleviate symptoms of sodium depletion and can have toxic effects; and (3) mice made sodium deficient for the first time begin drinking a sodium solution within 30 s of being given access to it, drink the bulk of sodium solution within 10 to 15 min of starting ingestion, and ingest an amount of sodium closely related to the extent of their sodium loss.[13] In summary, both basic systems for detection and control of ingestion of appropriate amounts of sodium seem to develop independent of prior experience of the beneficial effects of ingesting sodium when sodium deficient (for further review, see Schulkin[14]).

Of course, as is the case with any congenital motivational system, learning can increase the efficiency of appetitive[15,16] responses. For example, in a classic study of sodium appetite, Kriekhaus and Wolf[17] showed that rats that had learned while sodium replete to lever press for access to unpalatable solutions of sodium acetate or sodium phosphate would, when made sodium deficient for the first time, lever press vigorously, even if that behavior no longer resulted in access to sodium. Other rats given the same operant training, but with either potassium or calcium solutions rather than a sodium solution as a reward, made far fewer lever presses when made sodium deficient than did rats that had been trained to lever press for solutions containing sodium.

Taken together, the behavioral data clearly indicate that, when rodents are made sodium deficient, they experience an appetite for sodium salts.

## 3.2   PHYSIOLOGICAL EVIDENCE

Results of studies of physiological substrates of salt ingestion are consistent with the hypothesis that rodents have an inherent ability to respond adaptively to sodium depletion. For example, sodium-deficient rats exhibit a considerable decrease in excitation of sodium-responsive fibers in the chorda tympani in response to stimulation of the tongue with sodium,[18] and salt deprivation causes a marked reduction in the response of salt-sensitive cells in the nucleus tractus solitarus (NTS) as well as a substantial increase in the activity in response to salt on the tongue of cells in NTS that are normally responsive to sweet tastes.[19]

## 4   APPETITES FOR OTHER NUTRIENTS?

The responses of many animals to sodium depletion seem, as Richter[4] proposed, to rest on an innate, specific appetite. However, as Rozin and Schulkin[20] pointed out many decades later, it does not seem possible, as Richter[2] had also proposed, for dietary generalists (omnivores) to select a nutritionally balanced diet on the basis of specific appetites for each of the 30 to 50 macro- and micronutrients that they require.

## 5   DIETARY SELF-SELECTION

Results of Richter's studies of diet selection by rats given access to a cafeteria of 17 purified dietary components convinced Richter, and much of the academic community,[21] that animals had "a special appetite not only for salt and sugar, but also for protein, carbohydrate, sodium, calcium, phosphorus, potassium and the vitamins" (Richter et al.,[22] p. 744). The relatively uncritical acceptance of Richter's hypothesis concerning diet selection surely reflected, at least in part, acceptance of his assertion that laboratory demonstrations of an ability of animals to compose a nutritious diet by selecting from a cafeteria of foods only confirmed what could be deduced from the observation that animals survive in natural circumstances. "The survival of animals and humans in the wild state in which the diet had to be selected from a variety of beneficial, useless and even harmful substances is proof [emphasis added] of this ability...to make dietary selections which are conducive to normal growth and development" (Richter et al.,[22] p. 734).

## 6   COMMON SENSE AND EVOLUTIONARY THEORY

Evolutionary arguments contributed to acceptance of the hypothesis that animals have specific appetites for each nutrient that they require. Long before Richter began his empirical work, it had been argued that ecological pressures must have produced animals with "instinctive dietary habits" (Osborne and Mendel,[23] p. 20), with a capacity for "instinctive discernment inherited from a long line of naturally selected ancestors" shaped to select appropriate foods with "unerring precision" (Crichton-Browne,[24] p. 22). Consequently, although a few saw the importance of critically examining results of studies of dietary self-selection in animals (e.g., References 25 and 26), there was little perceived need to look closely at laboratory evidence consistent with the view that animals could self-select optimal diets. Such laboratory data demonstrated only what both evolutionary theory and naturalistic observation dictated must be true.

When rats in laboratory situations failed to self-select an adequate diet, as they often did,[21,26] such failures were interpreted[2] as the result of procedural artifacts of one kind or another: use of domesticated animals as subjects (though findings with domesticated animals were unobjectionable when those findings confirmed expectations), age-related exhaustion of an ability to self-select (though age of subjects was uncorrelated with success at self-selection),[26,27] or use of complex natural foods rather than purified food components in the cafeteria of foods offered to subjects

(though this put advocates of Richter's position in the logically awkward stance of having to argue that cafeteria-feeding studies using purified nutrients provided better laboratory analogues of foraging in natural circumstances than did studies using natural foods).

# 7   CAFETERIA-FEEDING EXPERIMENTS
## AND PROTEIN INTAKE

In the cafeteria-feeding experiments that Richter and others conducted, protein intake was the major determinant of growth rate and survival. As Scott[28] pointed out in 1946 (p. 403), rats in laboratory cafeteria-feeding situations "either do or do not like casein; if they like it, they eat an average of 3 grams a day and grow well; if they do not, they eat less than 0.1 gram per day, lose weight, and die within a short period."

In the classic experiments of Richter et al.,[22] rats were provided with two sources of protein and a relatively unpalatable carbohydrate.[7] Thus, the particular foods offered for choice by Richter et al.[22] may have led to relatively high protein intake by rats that chose foods on the basis of palatability alone. Perhaps as a result of this fortuitous choice of items by the experimenter, rats which were offered Richter's cafeteria of foods[28-30] survived and grew, though, as discussed in the penultimate section of this chapter, rats did not do so well in Richter's cafeteria-feeding situation as Richter and others thought that they did.

The relevant question, of course, is not whether an experimenter can choose an array of foods to offer in a cafeteria situation that ensures that subjects' flavor preferences cause them to ingest. To the contrary, the relevant question is whether, in general, animals will detect and select protein for ingestion on the basis of need when such selection is not assured by the relative palatabilities of available foods.

It is, in fact, almost embarrassingly easy to create situations in the laboratory in which rats are not able to select an adequate diet from among alternative foods. As the number of protein-poor foods offered together with a protein-rich food increases beyond one, the probability of adaptive food choice falls off rapidly.[31] As the time between ingestion of a nutritious food and the onset of beneficial effects of its ingestion increases,[32-34] and as the relative palatability of protein-rich foods decreases,[29,35] the probability of selecting enough protein-rich food to eat falls dramatically.

Consider a recent example. Beck and Galef[36] offered weanling and adolescent rats housed alone in large (1 × 1 m) cages a choice among four foods, three of which were low in protein (4.4% protein by weight, considerably less than the 12.5% protein generally considered adequate for young rats) and one that, although protein-rich (17.5% protein by weight), was relatively unpalatable. Subjects were given access to bowls containing each of the four diets for 24 h/day and an experimenter simply weighed each rat and each food bowl daily. Over a 7-day period, 14 of 18 subjects failed to eat substantial amounts of the protein-rich diet and failed to gain weight (as they should have at their ages), and many were seriously ill at the end of the 7 days.

The contrast with the behavior of subjects suffering sodium deprivation and offered salt solutions could not be more marked. Not only did protein-deprived subjects not immediately recognize and ingest appropriate amounts of protein, they did not learn over a period of a week to select the protein-rich food from among four alternatives by sampling among the four foods available and evaluating the postingestive consequences of their ingestion.

It is relevant to theoretical issues discussed below to note that 21 of 28 other weanling rats that shared their enclosures with older rats that the authors had trained to eat the protein-rich food thrived in Beck and Galef's[36] experimental situation. The behavioral mechanisms supporting this transfer of diet preference from knowledgeable rats to their naive companions are well understood[36] and involve a tendency, especially on the part of protein-deprived rats,[37] to show an enhanced intake of any food that they have smelled on the breath of a conspecific (for reviews, see Galef[38] and Galef and Beck[39]).

## 8 THEORETICAL IMPLICATIONS OF FAILURES TO SELF-SELECT

The failure of rats to gain weight in rather simple cafeteria-feeding situations was demonstrated numerous times in the literature[26,39] but largely ignored in discussions of dietary self-selection, taken together with the success of naive rats living together with knowledgeable conspecifics, seriously undermines Richter et al.'s[22] assertion, quoted above, that survival of animals in nature, where diets must be selected from among alternatives of varying nutritive value, proves that they can select diets conducive to normal growth and development.

When an area is colonized by members of some generalist species, the vast majority of immigrants may well fail to find foods that meet their nutritional needs and, consequently, may perish from malnutrition. However, should one individual, for whatever reason, stumble upon or learn to select an adequate diet, it will serve as a potential model for those that come after, greatly facilitating their search for a nutritious diet. As the results of experiments by Beck and Galef[36] described above indicate, presence of such models could make inhabitable otherwise uninhabitable areas.[39] Consequently, survival of animals in nature does not provide compelling evidence that individual animals can identify needed nutrients in natural environments.

Equally important, members of any species, even a species as far ranging as *Rattus norvegicus*, are not present everywhere within their species' range. Rats can survive only in those areas that provide, in accessible form, all resources necessary for life. If some portion of the environment contains a necessary nutrient only in a form that rats cannot innately recognize or learn to eat, that portion of the environment will be devoid of rats. Consequently, existence of omnivorous species in natural environments tells us little about the range of environments in which individual species' members can select a nutritionally adequate diet.

The message here is that results of studies of dietary self-selection must be examined far more critically than has been customary because failure to find success in diet selection in the laboratory is not, as Richter believed, indicative of a failure to capture in the laboratory the important features of a naturally occurring event.

## 9 LEARNING OR INSTINCT IN PROTEIN SELECTION?

Even in those cases where animals do come to select adequate amounts of protein from a cafeteria of foods, they appear to do so on the basis of their ability to learn to associate ingestion of substances with their postingestive consequences rather than on the basis of an innate, specific appetite for protein. The evidence that animals are able to associate a food flavor with its postingestional consequences, either positive[40] or negative,[41] is convincing, as is evidence that animals show potentially adaptive changes in their unconditioned responses to novel foods when they become ill.[42,43] Consequently, association learning can play an important role in development of adaptive patterns of diet selection in those laboratory situations that are neither so benign that innate palatability preferences lead directly to selection of nutritionally adequate diets, nor so demanding that only the presence of a knowledgeable conspecific can direct a newcomer to ingest foods containing needed nutrients. Harris et al.[31] provided deficient subjects that were unable to learn to identify the source of a necessary nutrient (in the Harris et al. experiment, vitamin B) in a cafeteria with an opportunity to learn about the positive consequences for health of ingesting the food in the cafeteria rich in vitamin B. The result was a marked improvement in subjects' subsequent performance in the cafeteria situation in which they had previously failed to consume a nutritionally balanced diet.

Learning, rather than instinct, almost surely provides the basis for much of whatever success animals have in cafeteria-feeding situations. Indeed, evidence of an important role of learning in successful diet selection was present even in Richter's earliest data on cafeteria feeding.[22]
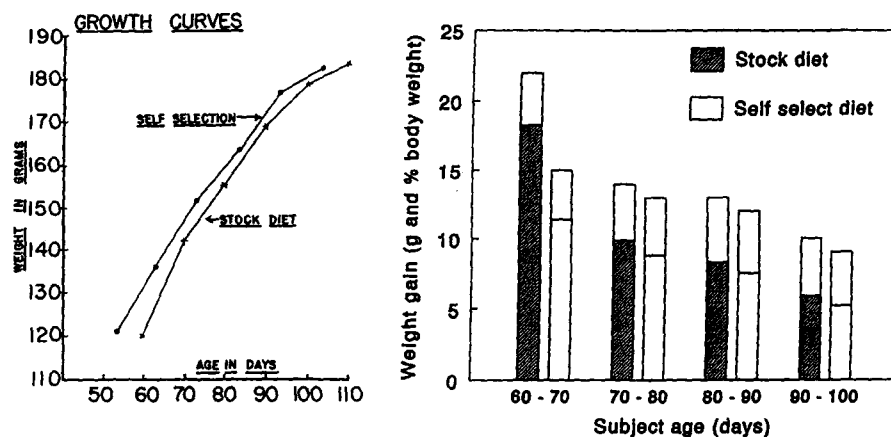
**FIGURE 1**   Left panel: average growth curves for 8 rats self-selecting a diet and 19 rats eating stock diet (Richter, 1942–1943, Figure 9). (From Richter, C. P., Holt, L., and Barelare, B., *Am. J. Physiol.,* 122, 734, 1938. With permission.) Right panel: mean change in body weight (total histograms) and in percent of body weight at 60 days of age (lower portion of each histogram) of rats either fed stock diet or allowed to self-select a diet over 10-day periods. Data calculated directly from the graph in the left panel.

## 10   RICHTER'S CLASSIC STUDY OF "TOTAL SELF-REGULATORY FUNCTIONS"

The data reported in Richter's classic papers on cafeteria feeding[2,22] seem to show that animals feeding from a cafeteria of purified ingredients select a highly nutritious diet without delay (left panel of Figure 1). The data, therefore, seem to provide support for the hypothesis that there exist specific appetites for each micro- and macronutrient present in the cafeteria and necessary for growth. However, if Richter had graphed his data differently, he might have reached a conclusion different from that which he did reach.

The left panel of Figure 1 reproduces Figure 9 from Richter's (1942–1943) paper on total self-regulatory functions.[2] It shows the average growth curves of eight rats given the opportunity to self-select a diet from a cafeteria of 17 purified ingredients, and of 19 rats maintained on the McCullom diet, a standard laboratory-rodent diet of the 1930s. The way the data are presented in the figure leads naturally to inference that rats can grow at least as fast when self-selecting a diet as when eating a stock diet, and can do so almost immediately after they are first placed in a situation where they are required to compose a diet for themselves from a multitude of ingredients. Indeed, Richter noted[2] that the cafeteria-fed rats grew at the same rate as those fed stock diet while consuming fewer calories.

The data plotted in Richter's figure are unusual in two respects: first, the ages at which rats in the two groups are weighed are offset by 5 days. This unusual procedure for data collection is important because subjects were growing rapidly throughout the experiment and subjects in the "self-selection" group that were weighed when 5 days older than subjects in the "stock-diet" group therefore seemed to be growing faster relative to subjects in the stock-diet group than they actually were. Second, members of the stock-diet group began the experiment at a considerably lower mean weight than did members of the self-selection group.

### 10.1   REANALYSIS OF THE DATA OF RICHTER ET AL. (1938)

Unusual features of the data in Richter's presentation can be corrected by examining the average weight gains of subjects in the two groups at comparable ages rather than their average absolute

weights at different ages. As the author did not have access to Richter's raw data, he first enlarged Richter's Figure 9[2] by 250%. He then used drafting instruments to find the points of intersection of the line segments indicating the mean weights of subjects in the self-selection group on the days when they were the same ages as were subjects in the stock-diet group when they were weighed. The author then calculated the increase in body weight of subjects in the two groups during successive 10-day periods. The results are plotted in the right panel of Figure 1.

There are two important features of the replotted data. First, from 60 to 100 days of age, subjects in the self-selection group gained less weight (approximately 49 g) than did subjects in the stock-diet group (approximately 59 g). As also can be seen in Figure 1, this difference between groups in weight gain becomes more pronounced if one corrects for the roughly 10% difference in body weight of subjects assigned to the two groups when they were 60 days old. Second, and more important, the performance of subjects in the self-selection group, relative to those in the stock-diet group, was particularly poor early in the experiment and improved as the experiment progressed. Early in the experiment, when subjects were from 60 to 70 days of age, subjects assigned to the self-selection group gained only 68% as much weight as did subjects assigned to the stock-diet group. Late in the experiment, when subjects were 90 to 100 days old, the corresponding figure was 88%. Such change in adequacy of self-selection of nutrients would be expected on the hypothesis that experience with the cafeteria of foods improved the ability of subjects in the self-selection group to compose a nutritious diet. Improvement in performance over days would not be predicted on the hypothesis that subjects had specific appetites for each necessary nutrient.

In summary, although rats feeding from the particular cafeteria of foods used in Richter's laboratory did unusually well,[26] even when feeding from that cafeteria the behavioral "wisdom of the body" was not so impressive as it was long believed to have been.

## 11   A CAVEAT

There is one important problem with comparisons between existing evidence of sodium appetite and existing evidence of protein appetite. The experimental methods used to study behavioral homeostasis in response to sodium and to protein deficiency have been quite different. Consequently, it is possible that the different pictures of control of sodium intake and protein intake that emerge from consideration of the literature may reflect, at least in part, methodological differences rather than differences in behavioral response to a lack of sodium or protein.

Students of sodium appetite first induce a deficit in their subjects, then expose their subjects to a cafeteria containing a source of sodium and one or more other nutrients. Subjects are not made sodium deficient in the choice situation and, when they are faced with a cafeteria of foods, they have only one problem to solve to return their internal milieu to its normal state; i.e., they have to identify sodium and ingest appropriate amounts of it.

Subjects in studies of protein appetite are usually placed, while still in homeostatic equilibrium, in a situation where they have a source of protein, a source of carbohydrate, a source of fat, and one or more sources of vitamins and minerals. Thus, subjects in studies of protein appetite usually develop a protein deficit while trying to solve a more complex ingestive problem than that presented to the typical subject in a study of sodium appetite.

It is possible that rats first made protein deficient, then given access to a source of protein and one or more protein-free foods, might behave like sodium-deficient rats given access to sodium in a choice situation. For example, Deutsch and co-workers[44] found that within 1 min of first being given a choice between a novel protein-containing diet and a novel carbohydrate, protein-deprived rats ate more of some proteins (soybean, gluten, zein, yeast, etc.), but not of others (casein or lactalbumin), than did protein-replete control subjects (also Heinrich et al.[45]). As Deutsch et al.[44] discuss at some length, the partial success of protein-deprived subjects in selecting proteins is both suggestive and problematic if one wishes to argue that rats have an innate ability to recognize protein.

It would be particularly interesting to repeat, using protein rather than sodium as a reward, the classic experiment on sodium appetite by Kriekhaus and Wolf[17] described above in the paragraphs concerning behavioral evidence of sodium appetite. The point of the repetition would be to determine whether rats made protein deficient for the first time have an unlearned motivation to secure protein similar to the innate sodium appetite they exhibit in response to first experience of a sodium deficit.

Given the difficulty that rats have in learning to ingest enough protein when placed in a cafeteria-feeding situation and the ease with which sodium-deficient rats find sodium in a cafeteria, it seems likely that the performance of protein-deficient rats in the Kriekhaus and Wolf[17] experiment would differ markedly from that of sodium-deficient rats facing the same circumstances.[46] However, the necessary experiment has not, to the best of this author's knowledge, been carried out.

## 12  CONCLUSION

The physiological processes internal to vertebrates have an impressive ability to maintain the internal milieu within limits compatible with life. In the case of some needed substances, such as sodium and water, the unlearned behavioral responses of the animal to imbalances in internal state are equally impressive. There is strong evidence of inherent mechanisms that act to motivate animals deficient in sodium or water[47] to ingest avidly the substance they need once it is encountered. Behavioral responses elicited by depletion of protein appear far less impressive. Naive animals seem to require extended periods of trial-and-error learning or interaction with knowledgeable conspecifics in order to identify protein-rich foods, and can do so only in a fairly restricted range of environments.[21,39] Even when given weeks in which to learn to select adequate amounts of protein-rich food from among an array of foods, rats fail as often as they succeed.[21,26] There is no compelling evidence of an innate-specific appetite for protein, and the absence of such evidence suggests that mechanisms for the neural control of protein selection are unlikely to exist.

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