Curt Richter and regulatory physiology

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Moran, Timothy H., and Jay Schulkin. Curt Richter and regulatory physiology. Am J Physiol Regulatory Integrative Comp Physiol 279: R357–R363, 2000.—Curt Richter made seminal contributions to our understanding of a number of issues regarding the relationships between physiology and behavior. He was the first to conceptualize behavior as an aspect of regulatory physiology. These ideas developed from his work on behavioral responses to a variety of physiological perturbations. The classic example is Richter’s demonstration of the development of avid sodium ingestion in response to urinary sodium loss after adrenalectomy. Some of Richter’s ideas on the nature and underlying physiology of specific appetites maintain their influence and continue to stimulate active investigation. Others, focused on abilities to self-select balanced diets, have not borne the test of time or experimental challenge. As current research takes a more molecular focus, Richter’s ideas on behavior in the service of the internal milieu maintain their currency, and the search for the molecular bases for these relationships should serve as a research focus.

sodium appetite; calcium appetite; self-selection; behavioral regulation

CURT RICHTER DIED IN 1989 after working in the same laboratory in the Department of Psychiatry at Johns Hopkins University School of Medicine for over 60 years. Shortly after Richter’s death, the extensive records from all these years of experiments were transferred to the Alan Mason Chesney Medical Archives. Richter had kept meticulous records on all the animals that were ever in his laboratory, documenting their activity, growth, and appetites throughout their life spans and in response to his experimental manipulations. In working with the Archives staff on ways of cataloging and preserving these extensive records, we had the opportunity to review some of the original data from Richter’s “self-regulatory function” experiments. In a series of experiments carried out during the 1930s and 1940s, Richter demonstrated that “the behavior or total organism regulators contribute to the maintenance of a constant internal environment” (18). This view of behavior in the service of homeostasis arose from his descriptions of a number of specific appetites. Richter’s methods for record keeping allowed us to go back and review raw data from his many experiments. Although 60-some years of records are still intact and available through the Alan Chesney Archives, access is not easy. Throughout his years at Hopkins, Richter never wanted work in the laboratory interrupted for painting or general maintenance. Consequently, by the time the laboratory was closed in 1988, paint that dated back to early 1920s was peeling from the ceilings and walls. All the records had become highly contaminated with lead dust. Each time we reviewed records, we had to put on protective clothing, face masks, and filtered breathing devices. Despite this inconvenience, the clarity of the experimental record was such that we could easily follow what had been done with each animal and how the behaviors of interest changed in response to the experimental manipulations. The answers the rats were providing to Richter’s questions were as clear as they had been over 60 years ago.

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In this review, we will recollect Richter’s contributions in this area and evaluate their present relevance. As the American Journal of Physiology begins its second century, it seems an appropriate time to reexamine concepts that arose during the first part of the 20th century and continue to influence the directions of current research.

CURT RICHTER THE SCIENTIST

As Richter himself recounted in an autobiographical chapter (19), he did not decide on a career in science until late in his education. Following his father’s wishes that he study engineering, Richter initially enrolled in a German technical school, Technische Hochschulen, in Dresden, in 1912. With the outbreak of the World War, Richter returned to America and enrolled at Harvard. His 3 years of study in Germany had only convinced him that engineering was not for him, and he began Harvard with no clear ideas for a course of study or an eventual career. After sampling courses in international diplomacy, economics, and history, he was finally attracted to the biological sciences through a series of lectures given by Professor E. B. Holt. In these lectures, Richter was introduced to the ideas of psychoanalysis and conditioned reflexes. This experience stimulated him to sign up for an experimental course in insect behavior given by Professor Robert Yerkes. This course greatly interested the young Richter, and it turned out to be the only course he took at Harvard for which he received an A. Yerkes introduced him to some of the ideas of John B. Watson, then a new professor of psychology at Johns Hopkins University. Richter read “snatches here and there” from Watson’s work on animal behavior and became convinced that he should try to work with Watson at the first opportunity.

After his graduation in 1917, Richter served in the Army for a 2-yr period. Still unsure of a career for himself when he mustered out in 1919, Richter recalled his desire to work with Watson. Richter arrived at Hopkins shortly after Watson had moved from the main campus to new laboratory facilities in the Phipps Clinic at the School of Medicine. On the basis of a brief interview, Watson accepted Richter as a student. Richter was given a room in the laboratory and told that he need not take any courses or attend lectures but that he was expected to produce a good piece of research. Richter was on his own to do as he liked. Richter credits this freedom of research with releasing “his gene” for experimental investigation. Richter quickly set up experiments of his own and, over the next 60-some years, produced over 375 papers.

Watson’s behaviorist ideas had very little influence on Richter. Richter was simply attracted by Watson’s interest in behavior as a field of study. Watson did not remain at Hopkins, and when Richter finished his degree in 1921, Professor Adolf Meyer, the Director of the Phipps Psychiatric Clinic, put Richter in charge of Watson’s old laboratory and provided support for Richter’s many research interests.

Richter’s first research project was a study of spontaneous activity in rats (15). Part of Richter’s genius was his ability to develop methods for quantifying behavior that were elegant in their combined effectiveness and simplicity. For his initial studies, Richter developed cages that sat on tambours covered with a rubber dam connected by rubber tubing to a small recording tambour such that even the slightest movement of the cage resulted in a mark on a smoked drum kymograph. This device enabled him to quickly recognize that spontaneous activity in the rats occurred in regularly recurring intervals. This initial finding led to a lifelong interest in periodic phenomena.

Richter’s interests quickly broadened, and he experimented with a variety of cages to allow him to routinely record food and fluid intake throughout the entire day and night in addition to activity. Eventually, Richter developed a standard cage consisting of two parts separated by the wall of a cage rack (24). The wall had a 3-in. opening, allowing the rat ready access between a running wheel and a living compartment. A microswitch connected to an event recorder tracked single revolutions of the running wheel. The living compartment could be of various sizes and could contain multiple drinking tubes and/or food cups. Drinking tubes were wired to record individual licks, and a device attached to the food cup registered eating times. These cages were in continuous use for >60 years.

Richter also developed a variety of standard procedures for data collection, display, and storage. Laboratory books were used for recording daily measurements and detailing experimental protocols. Each rat had a large chart showing daily activity and food and water intake, body weight, and, depending on the experiment, intake of specific nutrients or salts. Notations were often included to delineate times that surgeries were performed, cages changed, or to detail any equipment failures. Records from the event recorders were cut into small strips, one for each rat, and pasted on large sheets. These records allowed the easy detection of changes in a rat’s periodic activity or intake in response to experimental manipulations. When experiments were completed, charts were indexed, filed, and registered in an experimental library. These procedures made it possible for Richter to easily retrieve records from any animal.

Richter’s protocols for compiling and maintaining his data were an integral part of his overall experimental approach. His research focused on the responses of individual subjects to well-controlled manipulations. Whenever possible, animals served as their own control. Individual baselines were always firmly established, and behavior was closely monitored to identify the appropriate time for a change in a protocol. Richter himself reviewed the charts from individual animals weekly, and his methods allowed him to easily identify changing behavioral patterns. Richter’s publications reflect this overall approach. Data from individual animals are presented, showing representative responses to his manipulations. Group data are rare. Richter was concerned with big phenomena. If statistical manipu-
lations were necessary to demonstrate an effect, Rich-
ter was not very interested.

**SELF-REGULATORY FUNCTIONS**

As Richter’s research interests expanded beyond the study of periodic phenomena, his activities were greatly influenced by the late 19th century and early 20th century ideas of physiological homeostasis. Claude Bernard first described what he referred to as the internal milieu (2) and showed that the properties of this internal environment were ordinarily maintained within fixed limits. He had described some of the physiological mechanisms through which the body maintained these limits in the face of large alterations in external conditions. Walter Cannon, in an extensive series of experiments collected in his book *The Wisdom of the Body* (5), put forth the concept of homeostasis and the coordinated physiological processes through which an organism maintains an internal steady state. Both Bernard and Cannon focused almost entirely on physiological mechanisms for the maintenance of homeostasis. A major conceptual contribution of Richter’s was to expand this notion of the defense of the internal milieu to include behavioral or what he referred to as total organism regulators (18). For Richter, behavior was on a continuum with physiological events. Richter demonstrated the variety of ways in which behavior serves physiology in the regulation and maintenance of the internal milieu. He combined the perspective of Bernard with that of Cannon and he added behavioral regulation. Behavior for Richter was broadly conceived to include all aspects of identification, acquisition, and ingestion of those substances needed to maintain the internal environment.

Richter’s ideas about behavior in the service of the internal milieu stemmed from his experiments examining capacities for behavioral responses to the elimination of the normal physiological regulators. The classic example of such a behavioral capacity is the ingestion of salt (NaCl) after adrenalectomy. Adrenalectomized animals, lacking aldosterone, cannot effectively retain sodium. Therefore, large amounts of sodium are excreted in the urine and sodium levels drastically fall—a condition that is fatal. Administration of NaCl greatly reduces the symptoms of insufficiency and increases survival. Richter (16) discovered that rats who were adrenalectomized would ingest large quantities of NaCl even when it was provided in concentrations that would be avoided in intact rats. Under normal conditions, the conservation of sodium occurs mainly at the level of the kidney and its redistribution from gastrointestinal and bone reserves. However, in response to adrenalectomy, rats acquired a behavioral adaptation. They ingested sodium in quantities sufficient to maintain appropriate extracellular and intracellular sodium levels. As shown in Fig. 1, without access to sodium, animals die within a few days. In the presence of concentrated sodium solutions, the behavioral adaptation is revealed. Ingestion of the salt solution greatly increases after adrenalectomy, and survival rate is markedly increased. Richter referred to this increased sodium intake as a sodium or salt appetite.

Richter also demonstrated what he interpreted to be decreased taste thresholds for sodium solutions in adrenalectomized rats (17). In these experiments, rats had access to two bottles that initially both contained distilled water. Once intakes from each bottle had reached a constant level, one bottle was filled with a sodium chloride solution at what Richter estimated to be a subliminal concentration. Each day the concentration of sodium chloride was increased until rats demonstrated a consistent preference for the salt solution. The concentrations at which preferences were obtained

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**Fig. 1.** Increased sodium chloride intake after adrenalectomy. A: control rat without access to sodium chloride; B: experimental rat with a choice of water and 3% sodium chloride. Adapted from Ref. 18.
were compared in normal and adrenalectomized rats. The sodium chloride concentration at which adrenalectomized rats showed a preference for the sodium chloride solution over water was less than the concentration for normal rats. Richter interpreted these findings as indicating a change in taste threshold after adrenalectomy. Richter also felt that the preference for extremely small salt concentrations after adrenalectomy indicated that the altered appetite depended on chemical changes in the taste mechanisms rather than a learned response. He reasoned that the change in preference occurred before rats had the opportunity to discover the beneficial effects of ingesting large amounts of salt. Richter took this as evidence for the innate nature of salt appetite.

Richter found an analog for this salt appetite in the clinic (28). A young boy was admitted to Johns Hopkins Hospital showing marked development of secondary sex organs. Blood sodium and nitrogen content were low, but the boy did not seem especially ill. He refused the regular ward diet and, when force fed, he vomited on several occasions. Seven days after admission, the boy died. On autopsy, it was observed that his adrenals were large with hyperplasia of the androgenic cells and accompanying marked diminution of the normal cortical cells atrophied. Thus he was functionally adrenalectomized. After his death, letters from the boy’s mother revealed that the boy had a great craving for salt beginning at about 12 mo of age. In addition, because of constipation, he had been given saline enemas with regular frequency. The excessive salt consumption had evidently kept the boy alive. When he was brought into the hospital, he was not given free access to salt and, as a result, died.

Another classic example from Richter’s corpus on specific appetites is that of calcium ingestion in response to loss of parathyroid function. Richter (21, 22) demonstrated that parathyroidectomy resulted in tetany and eventual death when rats were maintained on a standard diet. However, when given access to a calcium solution, rats take sufficient quantities to keep themselves alive and avoid tetany. An example of this phenomena is shown in Fig. 2. Almost immediately after surgery, the rat’s consumption of a 2.4% calcium lactate solution increased so that by day 15, intake had increased to greater than 15 ml/day. Parathyroid implants in the anterior chamber of the eye reduced the calcium appetite to normal levels almost at once. Parathyroid hormone is an important regulator of calcium retention. In its absence, calcium is lost and a calcium deficiency results. Richter also noted that parathyroidectomy reduced intake of phosphorus solutions (18). This is in keeping with the reduced rate of phosphorous excretion in hypoparathyroidism.

Richter went on to demonstrate that pregnant and lactating rats would increase their ingestion of a number of substances, including sodium and calcium (20). As shown in Fig. 3, sodium chloride intake increased during the pregnancy and again during lactation, whereas the clear increase in calcium intake occurred during the postpartum period in response to the demands of lactation. Richter’s orientation was always within the purview of biological adaptation: the enhanced sodium and calcium ingestion during reproduction was serving maternal/fetal demands and the likelihood of successful reproduction.

Richter had suggested that each of these specific hungers had an innate basis. Richter’s nativism envisioned behavioral adaptation as a piece of innate engineering. Richter hypothesized that the body contained physiological systems for the detection of specific deficiency states, the detection of the needed mineral in the diet, and motivational systems ensuring the ingestion of the needed mineral (18). Richter believed that the detection of specific deficiencies activated specific hungers that resulted in alterations in gustatory acuity. Richter’s failure to consider a mediating role for learning mechanisms in these responses was a reflection of both his own scientific bias (he felt he could adequately explain the behavioral responses without invoking learning) and his own experiences with trying to poison rats. He had found that rats avoided poisons at concentrations that he considered to be well below those that might have any physiological effect. For him, the critical factor in poison detection was the natural taste of the poison rather than the possibility of the animal associating the taste with a negative consequence. Conditioned taste aversions had not yet been demonstrated (11), and Richter evidently did not consider the possibility that extremely low poison concentrations could be producing a mild malaise that the rats were associating with the taste.

Many aspects of Richter’s overall view on the mechanisms underlying mineral appetites have proven to be correct. Distinct physiological mechanisms for the detection of Na\(^+\) or Ca\(^{2+}\) do exist, and these mechanisms continue to be an area of active research interest. Physiological changes do occur in the gustatory system in response to sodium or calcium depletion. For example, alterations in calcium gustatory sensitivity, although relatively small, have been documented in re-
response to changes in overall calcium status (12). Rats maintained on a low-calcium diet had lower electrophysiological thresholds and increased chorda tympani responses to low concentrations of CaCl$_2$ and calcium lactate solutions. These rats also had reduced chorda tympani responses to high CaCl$_2$. Alterations such as these may enhance the animal’s ability to detect low calcium concentrations and increase the palatability of high Ca$^{2+}$ concentrations that are normally avoided. Both of these changes would facilitate calcium ingestion in response to deficiency. These changes are specific, in that Ca$^{2+}$-deficient rats did not have altered gustatory responsivity to NaCl.

The pattern of changes in gustatory physiology produced by Na$^+$ deficiency is more complex. Initial experiments by Contreras and colleagues (7, 8) demonstrated reductions in chorda tympani responses to high Na$^+$ concentration similar to those found for high Ca$^{2+}$ concentrations. However, unlike with Ca$^{2+}$, sodium deficiency did not influence the response to low Na$^+$ concentrations—a response predicted from Richter’s experiments (16) on “taste-thresholds.” Similar results were obtained by Scott and colleagues (13) examining responses to sodium in anesthetized sodium-deprived rats in the nucleus of the solitary tract (NTS), the brain site of termination of primary gustatory afferents. Responsivity to Na$^+$ in salt-sensitive cells was profoundly depressed in salt-deprived rats. However, this effect was partially offset by a 10-fold increase in activity in sweet-sensitive neurons to sodium. This lack of an increased electrophysiological response to low Na$^+$ concentrations and the altered responsivity of sweet-sensitive NTS cells suggested that the increased consumption of low Na$^+$ concentrations in response to salt deprivation that Richter demonstrated arose not from heightened detection but from changes in the hedonic value of the tasted sodium.

Recent experiments by Norgren and colleagues (14, 26) have suggested that both the method of sodium depletion and whether the animals are awake or anesthetized may significantly affect the pattern of results. Dietary sodium restriction resulting in a significant sodium appetite reduced NTS gustatory activity for Na$^+$ as well as for sucrose, citric acid, and quinine without altering the profile of taste neurons in awake behaving rats. In contrast, repeated sodium depletion with furosemide resulted in increased responses to Na$^+$, especially in those neurons that responded better to NaCl than to other stimuli in anesthetized rats. Thus enhanced sodium appetite can exist under conditions where the responses of peripheral and central taste neurons to sapid solutions are blunted, as occurs with dietary deficiency, or where the responses to sodium are enhanced, as with furosemide-induced sodium depletion. These data suggest that the avidity for Na$^+$ and the apparent change in its hedonic quality in response to Na$^+$ deficiency do not easily map onto changes in either the peripheral receptor or transduction mechanisms at early levels of processing.

Altered hedonic responses to salt in Na$^+$-deprived rats are substantiated in taste reactivity tests. Sodium-deprived rats change their orofacial response to hypertonic NaCl from a negative gape and chin scraping response to a more positive expression and do so on the first exposure to sodium salts after their first bout of sodium deficiency (3).

Although some of Richter’s predictions of how sodium or calcium deficiency altered taste responses have been demonstrated, his ideas regarding the degree to which alterations in responsivity were specific to the depleted substances were too narrow. Sodium-deficient rats, the paradigmatic example of an innate specific hunger, will on occasion ingest non-sodium salt solutions and, as stated above, altered taste response to many solutions in response to sodium depletion have been noted (9, 14, 29). Also, calcium-deficient rats do avidly ingest sodium (6, 27). Perhaps a more viable understanding of an innate specific hunger is an orientation to certain kinds of substance and the existence of regulatory mechanisms to detect, digest, and

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**Fig. 3. Changes in mineral ingestion during pregnancy and lactation.**

- **A**: sodium chloride (3%);
- **B**: calcium lactate (2.4%);
- **C**: sodium phosphate (8%);
- **D**: potassium chloride (1%).

Adapted from Ref. 18.
use the acquired substance in the regulation and maintenance of the internal milieu.

Perhaps the most controversial of all of Richter’s self-regulatory work was his demonstrations of extensive dietary self-selection. In a series of experiments, Richter offered rats a wide range of purified nutrients and minerals to determine whether the animals had the ability to appropriately select what they required for normal growth and development (20, 23). He found that rats would self-select adequate amounts of the nutrients and minerals to maintain a homeostatic balance. Richter interpreted these data as illustrating a capacity for dietary selection that could be deduced from the survival of omnivores in the natural world—if they did not have the ability to self-select a balanced diet, they would not have survived (18). Thus, when omnivores failed to self-select an adequate diet in some situations, the failure was interpreted by Richter as arising from some artifact of experimental design, such as the use of complex foods rather than pure chemical substances, inherited defects in sensory systems in domesticated animals, breakdown of systems with age, or, in human experiments, cultural influences leading children to distrust their own natural appetites.

Richter’s interpretations of the generalizability of the results from his cafeteria experiments have been extensively challenged (1, 10, 25). In many experimental situations, animals do not choose an optimal diet. This is especially the case for omnivores. Palatability factors help determine choice, concentrations of solutions, etc. (10, 25). Learning mechanisms often contribute to dietary choices. Rats readily learn the consequences of ingesting particular substances. Such consequences can produce either learned aversions or learned preferences. Furthermore, animals can also acquire dietary preferences from their social situation. Weanling animals who do poorly when presented with a self-selection diet, readily acquire a preference for a protein-adequate diet when it is presented in the presence of adults previously trained to ingest it (1). Data such as these show the limits of innate mechanisms in diet selection and highlight the role of learned mechanisms in dietary choices.

SUMMARY

Richter’s contribution to our overall understanding of the role of behavioral mechanisms in the maintenance of homeostasis was seminal. He was the first to view behavior from a regulatory perspective, and he provided experimental evidence that rats and humans could regulate the internal milieu in a number of contexts in which behavioral changes played the dominant role. Richter’s ideas continue to influence experimental work on mineral appetites. Many of his predictions on the nature of the controls of sodium and calcium appetite have proven to be correct. The extent of the impact of Richter’s ideas has been such that, other than in the area of mineral appetites, his ideas are taken for granted and his contributions are no longer acknowledged. The interactions between behavioral and physiological mechanisms in the maintenance of the internal milieu are widely accepted in many other domains.

In the current age of molecular biology and genetics, maintaining a perspective on the nature of interactions between behavioral and physiological processes is again important. If we are to successfully identify how gene products regulate the internal environment, we must include a consideration of behavioral processes. Richter understood that behavior was an integral feature of regulatory physiology and this understanding should continue to guide our current research endeavors.

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The Psychobiology of Curt Richter, edited by Elliott Blass, is an excellent starting point for obtaining a view for the range and depth of Richter’s work (4).

REFERENCES


