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The Principle of Regulation in Biology – From Bone to Eating Behavior

Abstract

Cell physiology and molecular biology typically follow a reductionistic approach in science. In the last decade, molecular principles and pathogenetic factors involved in the development of many diseases have been successfully discovered. Therefore, early biological concepts based on systemic and cybernetic thoughts have been largely overshadowed by these more recent molecular and pathogenetic factors. This review highlights discoveries on bone development and hypothalamic controlled feeding and eating behavior with a cybernetic and systemic perspective. Interestingly, ancient ideas on bone development and hypothalamic function are still reasonable considerations to embed new molecular discoveries into a systemic concept of principles organizing nature.

Key words
Cybernetics · mechanostat · estrogens · bone · eating behavior

Abbreviations

LHA	lateral hypothalamic area
VMH	ventro-medial hypothalamus
MFB	medial forebrain bundle
ARC	arcuate nucleus
PVN	periventricular nucleus
DMN	dorsomedial nucleus
NTS	nucleus tractus solitarius
CCK	cholecystokinin
MCH	melanin-concentrating hormone
POMC	pro-opiomelanocortin
5-HT	5-hydroxytryptamine
NPY	neuropeptide Y
αMSH	alpha-melanocyte-stimulating hormone
PTH	parathormone
LH	luteinizing hormone
SSI	strength strain index

Introduction

The present review follows the purpose to discuss the value of systems-theoretical thinking for the understanding of biological processes and especially for the pathogenesis of human diseases in detail. In the first part, the development of systems-theoretical thinking is reviewed in a general way under a historical point of view. Secondly, a short introduction into the concept of regulation provides the necessary terminology of system-control, which is discussed exemplarily for two processes in human biology: 1.) The adaptation of the skeletal system to biomechanical challenges and 2.) the process of body weight control. The reflection of biological structure and function by systems-theoretical

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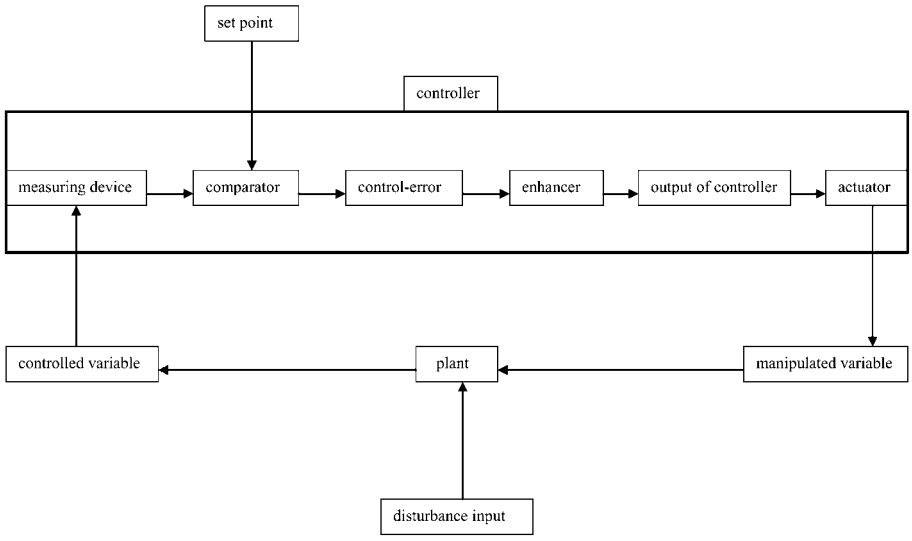

Fig. **1** The organization of a feedback loop in a cybernetic system. The controlled variable is compared to the set point. The difference is called control-error and enhanced by the controller. The enhanced error presents the input to the actuator which increases or decreases the manipulated variable. The manipulated variable changes the controlled variable, which is input for the controller again.

concept is not a new approach in science. But the introduction of modern genetic and molecular biological methods into biomedical research started a revolution in our understanding of many diseases in the second half of the 20th century. Diseases became understandable by identification of pathogenesis-related genes. Sometimes, even single genes could explain severe and fatal human diseases (i.e., phenylketonuria). Thereby, functional concepts of pathogenesis stepped into the background, because new discovered proteins entered the stage of scientific discourse and transported hope to understand biology under the simple reductionistic concept (bottom-up approaches) of causality (Sorger, 2005).

The Historical View: Bottom-up Approaches in Contrast to Top-down Thinking

The discourse about the interaction of methods and results in scientific experiments has a long tradition in science. The development of new methods in empirical sciences led to new discoveries changing our scientific models and vice versa: new models changed the methodological approach to scientific problems. This principle was widely visible in the scientific discussion in the first half of the 20th century, mainly in the positivism-discourse. Philosophical discussions, led by Russell (Russell, 1919), Wittgenstein (Wittgenstein, 1961), and Frege (Frege, 1966), created the basis of methodological discussions about the relation between conjecturing, formal proof, and truth in science. Exemplarily, this discussion is represented by the antique Greek question: "Is the sentence true, when a man from Kreta says that all men from Kreta are not telling the truth?" Finally, we cannot decide if this sentence is true, when we only use the information present in this sentence for our decision. Goedel, also a member of the "Wiener Kreis", transferred this question on formal logical systems in general, and he delivered the proof that the application of a formal logical system cannot consistently describe a subject in its complete extent, when logical system and subject are based on the same axioms (Goedel, 1990). Bottom-up approaches in thinking are characterized by the premise that important insights derive from deep mechanistic understanding. In mechanistic models, events are connected by causality (e.g., "event B stringently derives from event A"). Therefore, Goedel's proofs about incompleteness and inconsistency of logical systems are valid for bottom-up approaches. In conclusion, bottom-up approaches cannot describe a system in its complete extent without violation of causality. In contrast, systems-theoretical approaches typically follow top-down strategies. Thereby, the advantage of systems-theoretical approaches is the recognition of emergence-effects. Emergence describes that the analysis of ensembles, comprising several independent subjects, might reveal characteristics of the system, which are invisible when all subjects of the ensemble are regarded separately. In conclusion, bottom-up approaches could be linked to cybernetic and systems-theoretical (top-down) approaches to yield multi-scale models combining detailed mechanism and wide biological scope (Sorger, 2005).

The Concept of Regulation: a Brief Introduction in the Cybernetic Terminology

Norbert Wiener published his book "Cybernetics" in 1948 which was the birth of a common theory of regulation (Wiener, 1948). Essentially, the terminus regulation can be described as the adaptation of a controlled variable to a given set point in a feedback loop. This process of adaptation is managed by the controller, which records the difference between the controlled variable and the set point (Fig. **1**). The time-related behavior to adapt the controlled variable to the set point might be described by three different scenarios. In the first scenario, the manipulated variable is proportionally changed to the measured difference between the controlled variable and the set point. Therefore, this kind of regulation is called "proportional control" and can be illustrated by the given example in Figure **2** which shows the regulation of the water level in a basin by a proportionally working algorithm. This type of control system is characterized by the inability to decrease the difference between the controlled variable and the set point to zero. When the response of the controller is dependent on the change of the controlled variable over time, the type of regulation is called differential control. In medicine,

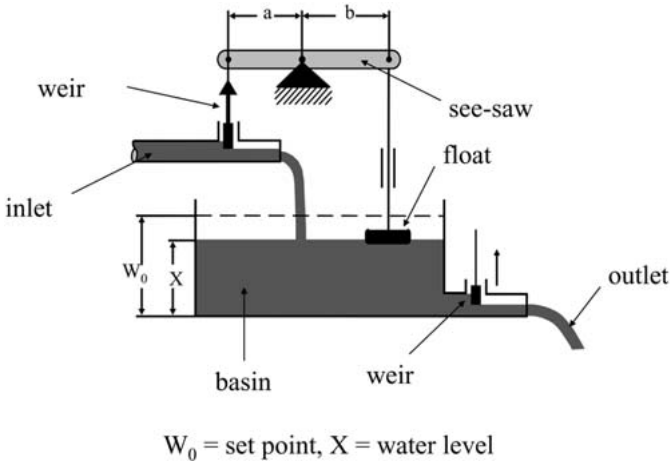

Fig. **2** The water level of the basin is regulated by a simple proportional control. The water level of the basin falls depending on the outlet flow. Therefore, the float moves nearer to the ground of the basin and pulls on the see-saw. The see-saw turns proportionally to the lowered water level to the side of the float. Thus, the weir controlling the inlet flow is elevated and the flow is increased proportionally to the decrease of the water level of the basin.

a well-known example is the induction of hypoglycemic symptoms by rapidly decreasing blood glucose levels, even when blood glucose levels are above the range of hypoglycemia. This kind of regulation is more able than the proportional control to hold the controlled variable near the set point as long as the change over time is small in relation to the time constant of the system, which describes the speed of reaction due to changes in the feedback loop. The third type of regulation can be called "integral control". The manipulated variable is changed in relation to the sum of changes over the time. The integral control serves the advantage to hold the controlled variable near the set point and is more robust due to larger changes over time than the differential control. The disadvantage of this kind of regulation is that it has a slower reaction to changes in comparison to both the proportional control and differential control mechanisms. Regulation in nature seldom follows one of these three classical mechanisms in a pure way. Rather, most systems can be described by a combination of these three basic scenarios. In this way, advantages of different control strategies are combined. For example, the proportional differential control combines the robustness of the proportional control with the precision of the differential control.

The competition for limited resources and therefore, the optimized adaptation of species to their environmental conditions is the main issue in Darwin's theory of evolution (Darwin, 1859). In a teleological sense, the issue of optimization obliges species to develop mechanisms which allow adaptation to the best fit to environmental conditions. However, this mechanism of adaptation is nothing else than the optimization of a variable in a feedback loop which can be described by one of the control patterns mentioned above. Therefore, the development of feedback loops might be a result of the selection pressure which is the driving force for phylogenesis on earth. An interesting question derives from the idea of internal evolutionary forces which has been already discussed to explain the redundancy of genetic systems in organisms (Dover, 2000). This concept means that the interaction between genomic turnover and natural selection leads to a molecular coevolution between interacting molecules and hence increases the diversity of phenotypes. Do we also expect the phenomenon of redundancy in feedback loops controlling food intake? Horvath speculates in his recently published article that redundancy is likely established for feeding regulation (Horvath, 2005). Therefore, pharmaceutical concepts to shortcut the CNS component of feeding regulation could be a promising approach for the therapy of diseases related to eating behavior.

The First Example: The Mechanostat Theory of Bone Development

Recently, the cybernetic concept has been applied to the concept of musculoskeletal interactions. Harold Frost revitalized the theory of Lucius Wolff to explain the development of our skeletal systems and the pathogenesis of bone diseases in dependence on biomechanical forces (Frost, 2004; Schoenau and Frost, 2002). This mechanostat theory describes geometrical characteristics of skeletal elements (e.g., cortical thickness, cross-sectional diameter) in dependence on environmental mechanical conditions, especially muscle force (Schoenau et al., 2003). In detail, the mechanostat theory and the theory of the "Muscle-Bone-Unit" are based on Frost's Utah paradigm (Frost and Schoenau, 2000). The first proposition defines controlled and manipulated variable of the cybernetic circuitry. Following the Utah paradigm, bone strain is the controlled variable and geometrical characteristics of the bone represent the manipulated variable. Because geometrical characteristics comprise bone size, which is related to bone mass, and proportion of the bone (e.g., cross-sectional diameter), bones with the same bone mass can have different bone strength. In example, a bone tube with a large diameter and a small cortical thickness can have a higher strength strain index (SSI), a measure of bone stability, than a skeletal element with a smaller diameter and larger cortical thickness (Schoenau et al., 2002). Therefore, bone mass taken as the lonely controlled variable in the system of bone adaptation to biomechanical forces does not lead to valid results in mammalian bone physiology. Bone mass and geometry of the skeletal element interact with each other and cannot be interpreted separately (Fig. **3**). The introduction of this concept into the pathogenesis of bone diseases led to a bunch of considerations about known pathogenetic agents of skeletal diseases. Seen from the perspective of a pediatric endocrinologist, we have to deal with questions like "Do estrogens induce bone formation?" or "Do corticosteroids induce bone resorption?". The analysis human data on the development of skeletal elements and muscle force delivered the proof that a simple proportional model of regulation could describe the relation between muscle force and bone strength. Interestingly, females have higher relation of bone mass to muscle force than males with the beginning puberty. Therefore, puberty increases the set point of bone to resist endosteal biomechanical stress in females, which is likely transmitted by estradiol (Schoenau et al., 2001). Moreover, females affected with amenorrhea have lower set points being demonstrated in young women affected with anorexia nervosa (Fricke et al., 2005). Those results are a reminder that we have to distinguish between signals modulating the feedback loop by change of the set point

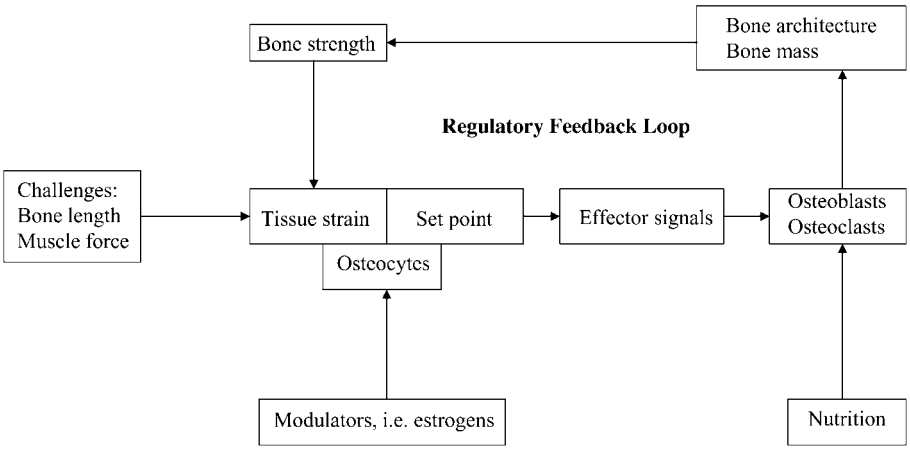

Fig. **3** A functional model of bone development based on mechanostat theory. The central piece of bone regulation is the feedback loop between bone deformation (tissue strain) and bone strength. During growth this homeostatic system in continually forced to adapt to external challenges. Hormones, e.g., estrogens, modulate the central regulatory system.

(e.g., estrogens), signals interacting with the actuator, osteoblasts, and osteoclasts (PTH, bisphosphonates), and signals affecting the plant (e.g., effect of corticosteroids on muscle force). Moreover, those results led to the establishment of the muscle/bone ratio as a new concept of diagnostics in pediatric osteology with remarkable influence on therapeutic strategies in bone diseases (Schoenau, 2005). Therefore, the treatment of osteoporosis with estrogens is reasonable, when mechanical stimuli are applied to the skeleton, because these hormones modulate the adaptation of bone to mechanical forces, but they do not induce bone formation. Furthermore, a therapy activating the musculoskeletal system can be successful, when resources of bone formation (e.g., calcium, phosphate, amino acids) are available and actuator cells can be functionally activated.

The Second Example: The Hypothalamic Control of Eating Behavior

Anatomy and molecular physiology of hypothalamic feeding regulation

The understanding of mechanisms regulating appetite, hunger, and food intake under the perspective of cybernetics requires the interpretation of biological structures as elements of a regulatory system. Classical experiments on the localization of appetite-regulating neuronal structures were performed in the middle and second half of the last century. In those experiments, the effect of lesions of hypothalamic areas on food intake and body weight was investigated. Bilateral lesions of the lateral hypothalamic area (LHA) induced aphagic behavior (Anand and Brobeck, 1951). In contrast, lesions of the ventromedial hypothalamus (VMH) resulted in a hyperphagic behavior (Duggan and Booth, 1986).

The "Dual Center Hypothesis" is based on those results of lesion experiments (Stellar, 1954). Stellar localized the generation of appetite in LHA and the feeling of saturation in VMH. Later, experimental results could not support this theory and discussed the basic foundations of the "Dual Center Hypothesis" in a different light. Lesions of the VMH increase the parasympathetic activity and therefore, augment insulin secretion (Steffens, 1970). Elevated insulin secretion induces hyperphagia and increases lipogenesis. Those symptoms of VMH lesions disappear when a vagotomy is performed (Inoue, 1978). Lesions of LHA stand in physiological contrast to VMH lesions. Bilateral lesions of the vagal nerve decreases parasympathetic activity and therefore vagal activity. Therefore, insulin secretion is decreased and the duration of digestion is increased resulting in a longer continuing feeling of saturation after food intake (Powley and Keesey, 1970). Moreover, lesions of the medial forebrain bundle (MFB), which is anatomically localized near to LHA, result in a neglect of appetite inducing sensoric stimuli (Marshall et al., 1971). Those dopaminergic fibers transmit the general sensitivity to sensoric stimuli (arousal). Therefore, lesions of the MFB reduce drive-dependent behavior which also includes feeding behavior (Ungerstedt, 1971). Moreover, serotonergic fibers, mainly afferent from the raphe nuclei, act on neurons involved in the hypothalamic control of food intake (Leibowitz and Alexander, 1998). Recently, 5-HT2 c receptors were described for alpha-melanocyte-stimulating hormone (α-MSH)-containing neurons of the hypothalamic neuronal network, which could be a target of serotonergic afferents (Heisler et al., 2002). This result could explain why selective serotonin reuptake inhibitors (SSRI) can be helpful in the pharmacological treatment of obesity (Ljung et al., 2001).

The discovery of peripheral feedback signals like leptin (Nunez et al., 1980; Friedman and Halaas, 1998) and ghrelin (Tschop et al., 2000; Horvath et al., 2001) allowed the discovery of hypothalamic and cortical cell populations that are involved in the regulation of food intake. The arcuate nucleus (ARC) represents a main target of leptin binding and lesions of this area result in hyperphagic behavior (Schwartz et al., 2000). In contrast, paraventricular and dorsomedial nucleus (PVN, DMN) of the hypothalamus are areas where cell populations are localized with appetite-inhibiting characteristics (Schwartz et al., 2000).

In addition to hypothalamic cell populations there exist neuronal structures with influence on feeding behavior. Vagal afferents transmit information about intramural gastric pressure and are in synaptic contact with neurons of the nucleus tractus solitarius (NTS), which project to the LHA (Schwartz et al., 2000). Moreover, the peptide hormone cholecystokinin (CCK) possesses appetite-reducing characteristics in interaction with neurons of the NTS (Geary, 2000). Interestingly, this appetite-reducing effect is enhanced by estradiol (Geary et al., 2001). Thereby, estra-

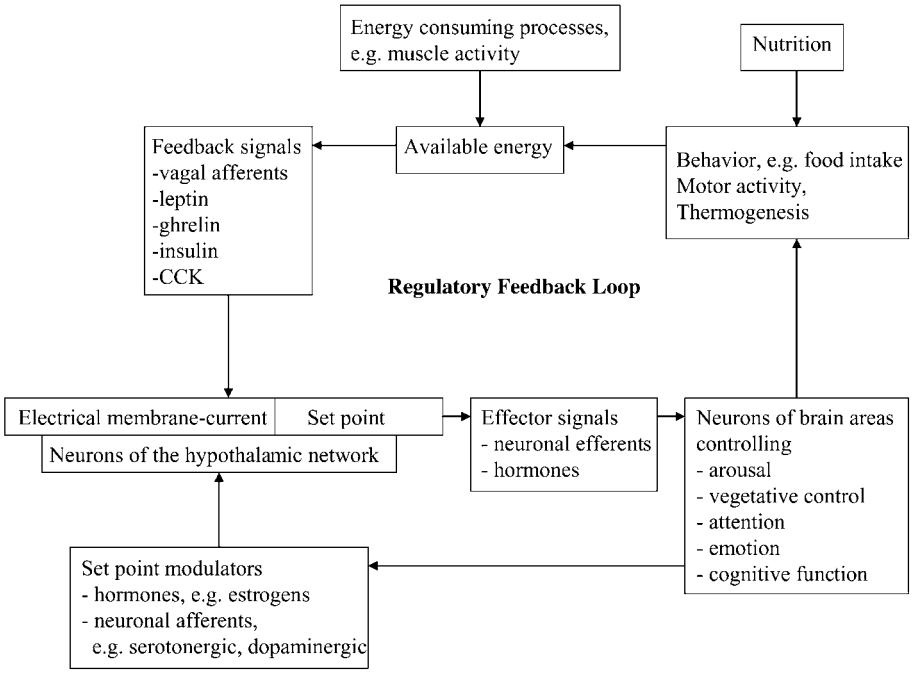

Fig. **4** A systemic approach to feeding and eating behavior. The model integrates recently published data on molecular aspects on the control of food intake into a cybernetic model.
Exemplarily, the set point is represented by electrical membrane-currents (EPSC, excitatory postsynaptic current; IPSC, inhibitory postsynaptic current) of hypothalamic feedback neurons (orexigenic or anorexigenic). The set point is modified by hormones, e.g. estradiol, or neuronal afferents, e.g. serotonergic afferents. Feedback neurons integrate homeostatic and sensoric information and send efferents to neuronal networks organizing behavior and homeostasis (actuator networks).

diol decreases the amount of ingested food per meal, but does not affect the number of meals.

Moreover, intracerebroventricularly administered estrogens inhibit food intake. In addition, the cerebral infusion of androgens also possesses an inhibiting effect on food intake, but only after aromatization to estrogen (Nunez et al., 1980). In contrast, the systemic application of androgens mainly induces anabolic effects transmitted by skeletal muscles (Rand and Breedlove, 1992). Because hypothalamic neurons possess a high number of binding sites for estrogen, the modulation of feeding behavior over a direct mechanism on hypothalamic neurons can be suggested (Krieger et al., 1976). This was emphasized by the discovery that estrogens decrease melanin-concentrating hormone (MCH) expression in orexigenic neurons of LHA (Mystkowski et al., 2000; Morton et al., 2004). Moreover, estrogens modify electrical properties of pro-opiomelanocortin (POMC) expressing anorexigenic neurons over a recently discovered G-protein coupled membrane receptor (Qiu et al, 2003; Kelly et al., 2003). The effect of estradiol on the food intake inhibiting signal CCK was already discussed above and indicates a second redundant pathway how estradiol modulates feeding behavior (Geary, 2000; Geary et al., 2001).

The cybernetic concept of hypothalamic feeding control

In a cybernetic model, hormones (like leptin, ghrelin, and insulin) and neuronal afferents (i.e., vagal afferents) represent controlled variables, which transmit the feedback of the manipulated variables body mass, body composition, digestion, metabolism, and thermogenesis. As mentioned above, vagotomy can partly inhibit the effect of hypothalamic lesions on feeding behavior. Therefore, signals of the actuator are partly transmitted by parasympathic efferents, which are under the control of the LHA and VMH. In conclusion, the hypothalamus represents a sensor and partly functions as the actuator in a control system of feeding behavior. Estrogens and monoaminergic afferents cannot provide the function of enhancement on feedback signals of food intake, because in this case, the control error is enhanced independently from the sign of error (positive or negative). Then, the directional effect on feeding behavior, enhancement, or inhibition, of estrogens and monoamines is not explainable. More likely, estrogens and monoamines change the set point of the controller. In this way, a directional effect on feeding behavior becomes explainable, because the feedback loop drifts to more or less food intake. Interestingly, the alteration of set points of body weight control becomes visible in consideration of diseases related to high loss of weight and body fat content. Serum leptin levels are in tight relation to body fat mass. Therefore, decreasing leptin serum levels indicate a reduction of the body fat mass. In contrast, increasing leptin levels characterize an augmentation of the body fat content (Kalra et al., 1999). Interestingly, the described relationship between leptin and body weight is altered in females affected with anorexia nervosa. In contrast to weight loss, those females show higher leptin serum levels at the same body weight when they gain weight, which is a significant risk for the occurrence of relapses (Mantzoros et al., 1997; Holtkamp et al., 2004). Therefore, a change of the set point can be suggested for the current anorexic episode which even affects the recovery of these individuals.

The modus of control is an interesting issue in the discussion about the regulation of food intake as well. It can be assumed that issues with the need of fast physiological control, (e.g., the glucose serum level in minutes), are controlled by the modus of differential control. In contrast, the regulation of body fat mass needs a robust and more noise insensitive control, because body weight is adapted in a larger time period of days. Therefore, proportional or integral control provides an advantage in the regulation of body weight.

In conclusion, recently published results elucidate the physiological process of homeostatic control of body weight on a molecular level. Interestingly, those novel results on neuronal networks in the hypothalamus revitalize ancient concepts of the

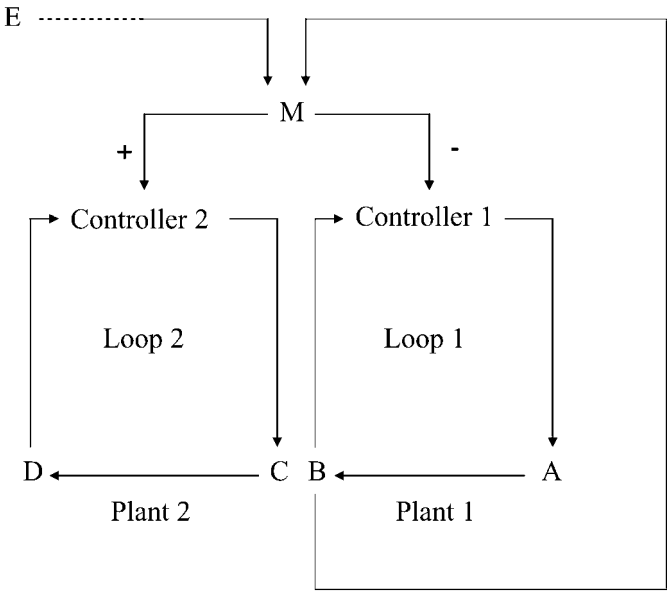

Fig. **5** Two feedback loops chained to a metamodel of regulation. The construction of a metamodel of regulation is exemplarily described for the control of feeding behavior and mating behavior. Variables A (food intake) and B (leptin), C (lordosis behavior) and D (sensoric stimuli due to mounting behavior), respectively, are manipulated and controlled variables of feedback loop 1 (control of food intake), respectively feedback loop 2 (control of mating behavior). The set points of the controllers are modulated by variable M (estradiol). Thereby, set points are influenced in opposite directions. Moreover, the modulator is influenced by an additional variable E (e.g., luteinizing hormone, LH) and also in feedback by variable B (leptin). Therefore, variable B is also member of a further feedback loop: B → M → Controller 1 → A → B.

regulation of food intake and provide a plea for a more systemic approach to biological concepts of feeding behavior (Fig. **4**).

Conclusion

The description of physiological processes by a cybernetic model attributes variables of a control system to biological structures, whereas manipulated and controlled variable are connected to each other by a transfer function. The attribution of control elements to biological structures always contains the problem of semantic simplification, because the biological structure is reduced to a singular meaning. The same biological structure can be a controlled variable in a certain feedback loop and a manipulated variable in a different loop. Therefore, feedback loops might be organized in chains, where elements are parts of different loops in different functions. The present data about the effect of estrogens and monoamines on feeding and mating behavior in rodents support this consideration on chained loops to metamodels of regulation (Fig. **5**). Serotonergic agonists facilitate mating behavior (Nedergaard et al., 2004), whereas serotonergic afferents to the ARC inhibit feeding behavior (Leibowitz and Alexander, 1998). In addition, estrogens inhibit food intake and facilitate mating behavior (Geary, 2000; Geary et al., 2001; Mong and Pfaff, 2003). Therefore, serotonergic afferents and estrogens organize the integration of two chained behavioral feedback loops, feeding and mating behavior, in one behavioral performance. Coming back to human physiology, physicians can draw an essential conclusion from the application of systems-theory to human diseases. If diseases are not based on a simple chain of causality, the pathophysiological description under systems-theoretical aspects will be helpful to identify a successful therapeutic strategy. As mentioned above, this concept was exemplarily established by the introduction of the muscle/bone ratio in pediatric osteology. Regarding obesity and eating disorders, the description of human physiology resembles to be much complex than for the skeleton. This aspect is underlined by the high recidivism rate in the treatment of obesity and psychiatric eating disorders (Levin, 2004). Nevertheless, the identification of key players in the system of metabolic control is the first important step to develop physiological models, where emergence might increase our understanding of principles organizing nature (Sorger, 2005). Thereby, ancient concepts of regulation might serve as useful basis for the interpretation of novel discoveries. In the future, the integrated use of methods of cell biology and classical physiology under the reflection of systems-theory might reveal more hidden secrets in the biology of mammals and humans.

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