

# Pavlovian influences over food and drug intake

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## Abstract

Consuming food and taking drugs share several important characteristics. In particular, each causes changes in important physiological parameters that are constantly being monitored and regulated by the brain. As examples, blood glucose increases after meals; and body temperature decreases after ethanol is taken. Such changes elicit neurally-mediated homeostatic responses that serve to reduce the magnitude and duration of the perturbation. It is argued that when an individual can accurately anticipate pending meals or drugs, it can make appropriate responses to minimize or totally neutralize the meal/drug-elicited perturbations. This phenomenon, which is the basis for meal and drug tolerance, relies upon Pavlovian conditioning. Literature is reviewed which documents the role of conditioning processes in the development of tolerance. The argument is made that conditioned responses enable individuals to derive necessary or desirable aspects of food and drugs while minimizing some of their negative effects. In a final section, drug tolerance is discussed as a natural consequence of evolution-derived, meal-related learning processes, with associated negative consequences. © 2000 Elsevier Science B.V. All rights reserved.

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## 1. Introduction

In order to survive, organisms have evolved complex systems that enable them to cope with variable sources of energy, water, micronutrients and threats from the environment. One strategy has been to create, isolate and maintain an internal environment with optimal levels of critical parameters such as temperature and osmolality. As a result, buffered within this internal environment, bodily processes function efficiently in spite of changing external conditions. Constancy of this internal environment is achieved via an interrelated series of regulated systems, each responsible for one or more key parameters, and the overall process is called homeostasis [6]. Physiological regulatory systems have several features that are germane to the present discussion. For one, they are sensitive to the level of the parameter in question. And whereas regulation can

occur at the level of single cells or tissues as well as at a more global level via the nervous system, it is only the latter that we are addressing in this review. Finally, regulatory systems direct a broad array of responses that control the level of the key parameter. Hence, a regulated system can initiate neural responses when a change occurs and is detected in a monitored parameter. The conclusion that we shall make in this review is that when individuals are able to predict accurately that a regulated bodily parameter is going to be altered by an external event, they can learn to initiate a conditioned response in anticipation of the perturbation that minimizes its impact. We believe that this general learning mechanism is an integral component of any centrally regulated system. We further believe that the existence of anticipatory conditioned responses allows the organism freedom to behave in a complex environment while minimizing homeostatically disruptive events.

In this review, we will compare and contrast two behaviors, eating and drug taking, because each presents challenges to regulated bodily systems and each relies upon centrally-mediated anticipatory conditioned

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responses. These responses are of course subject to the general laws of learning, and classical or Pavlovian conditioning is their primary mechanism. Ingestion of food is a ubiquitous and requisite behavior. Nonetheless, we believe that the well-adapted individual relies upon classically-conditioned ingestion-relevant responses for optimal functioning [46,52]. In contrast, drug taking is an aberrant behavior, and we argue that classically-conditioned responses develop with repeated drug use and play a prominent role in the etiology of drug tolerance and addiction [29].

## 2. Regulatory implications of food and drugs

Both drugs and food, when they enter the body, interact chemically with numerous ongoing and well-controlled biologic processes. Drugs are taken primarily because of their pharmacological effects, and the term ‘pharmacological’ itself implies an ability to interact with various cellular processes. Food provides calories in the form of macronutrients (carbohydrates, fats and proteins) as well as necessary micronutrients (vitamins and minerals), osmoles and water. The digestive process converts ingested food into small absorbable molecules that enter the blood and consequently interact with and alter the chemical milieu of the body. While many of the consequences of taking food or drugs may be quite desirable, some of the biochemical changes associated with their consumption may not be. As a simple example, when alcohol (ethanol) is consumed, there may be (presumably desirable) changes of mood or perceived stress that are desirable to the individual, but there are also changes of motor coordination, and autonomically controlled parameters such as body temperature, that are not. Likewise, whereas many aspects of eating are desirable, and necessary nutrients are supplied that ultimately provide energy and growth, eating also causes changes of temperature, of osmotic pressure, and of highly regulated and tightly controlled blood compounds (e.g. blood glucose). We suggest that through the process of Pavlovian conditioning, individuals are able to maintain the desirable aspects of taking food, and sometimes drugs, while simultaneously minimizing necessary but less desirable negative side effects of each. As an example, to the extent that calories and other necessary nutrients can be ingested without eliciting changes of temperature or blood glucose or other autonomic parameters, potential problems associated with meal taking can be minimized. Hence, conditioned responses that are elicited during meals and that preclude extreme changes of temperature and other parameters enable individuals to consume sometimes quite large meals. This in turn provides the individual with flexibility as to when meals occur and are integrated with its other behaviors [52].

## 3. Biological consequences of meal taking

Over the past half-century or more, the predominant view concerning the reason that individuals initiate meals (i.e. that they experience and respond to ‘hunger’) is that the level of available fuel for energy in critical tissues is low. Hence, Mayer’s glucostatic hypothesis [24,25] posited that meals are initiated when glucose utilization by key sensory cells in the hypothalamus reaches a low threshold. Eating in turn was viewed as replenishing the dwindling supply of glucose and consequently turning off the meal. The appeal and lasting value of the glucostatic hypothesis lay in its simplicity. The brain was recognized as being somewhat unique among organs in requiring a constant supply of energy in the form of glucose from the blood, such that even a short disruption in the continuous glucose stream compromises brain functioning and can quickly result in coma and death. All that seemed necessary therefore was a group of neurons whose electrical signaling to areas controlling eating (or ‘hunger’) is proportional to glucose availability. Hence, low available glucose (‘depletion’) could be rapidly translated into a signal to find food and eat, and restoration of the glucose stream (‘repletion’) would turn off the system. In a nutshell, that describes the glucostatic hypothesis [24,25]. Depletion-repletion models, including the glucostatic hypothesis as well as others based upon proteins, or body temperature, or total available energy to key tissues, remain attractive because of their simplicity and appeal to common sense.

In actuality, there is scant evidence that depletion of one or another source of fuel or energy dictates the onset of most bouts of eating under normal circumstances. For although it is true that experimentally-induced reductions of available carbohydrate or fat can cause animals or humans to eat, the necessary reductions are far greater than are observed in freely feeding individuals (see Refs. [13,16]). Further, any increase of plasma glucose derived from newly ingested food would be too slow to ‘replete’ a dwindling energy supply. This is not to imply that when glucose (level or utilization in specific areas of the brain) is reduced, homeostatic responses are not recruited. To the contrary, low glucose initiates a series of regulatory responses including increased secretion of epinephrine from the adrenal medulla and increased sympathetic input to the pancreas and liver [17,30,36]. These in turn cause an instantaneous secretion of endogenous glucose into the blood. Hence, low glucose availability is countered by a rapid and efficient infusion of endogenous glucose. Eating, on the other hand, should not be considered an adaptive solution to a short-term shortage of glucose. If eating is to be considered a ‘homeostatic’ behavior, the argument can be better made that it is a response to a reduction of the body’s fat stores (see Refs. [31,52]).

Nonetheless, eating and glucose availability are intimately related, but the interrelationship between the two is based upon post- rather than pre-prandial glucose. Blood glucose rises after meals as ingested carbohydrates pass out of the intestine. Hence, food intake causes a necessary perturbation in a tightly regulated parameter, and the body appropriately makes several responses to cope with the post-prandial hyperglycemia. As examples, insulin is secreted from the pancreas and less endogenous glucose is secreted into the blood from the liver. One consequence is that post-prandial elevations of blood glucose are reduced. Nonetheless, if these reactive responses were all that occurred, individuals would experience quite large bouts of hyperglycemia every time they ate, and the severity of the perturbation would increase with meal size.

Fortunately, there is an alternative line of defense against ingestion-related increments of glucose. A large literature suggests that stimuli associated with meals elicit insulin secretion in animals, and that this response greatly reduces the post-prandial increase of glucose that would otherwise occur (see reviews in Refs. [46,47]). The reflex has been well characterized. Food-associated cues, such as tastes or odors, initiate activity in the brain that ultimately passes via the vagus nerve to the pancreas, where released acetylcholine releases insulin [27,37,49]. If the response is prevented, for example by cutting the vagus nerve [21,45], denervating the pancreas [15,21,37], or blocking the action of acetylcholine pharmacologically [37,45], postprandial glucose levels are increased and resemble what occurs in individuals with diabetes mellitus. This meal-associated insulin secretion is called cephalic insulin because the impetus for its activation comes from the brain rather than via glucose in the blood stream.

Importantly, we have found that cephalic insulin can be brought under stimulus control through classical conditioning [47–51]. That is, when arbitrary stimuli (odors, sounds, time of day) are reliably associated with food, those arbitrary stimuli acquire the ability to elicit insulin secretion via the vagal pathway from the brain [45]. We further found that the response is not secondary to pseudoconditioning or sensitization and that it undergoes extinction when the eliciting stimulus is presented by itself [18,50]. The important point is that when an individual is confronted with stimuli implying that food in the gut is imminent, they begin secreting insulin prior to any actual entry of newly ingested glucose into the blood and thereby circumvent a larger increase of plasma glucose.

When blood glucose is continuously monitored by attaching a rat's vein to a glucose analyzer, rats are found to have a small but reliable decrease of glucose prior to every spontaneous meal [2,4,5,22,52]. Importantly, the decrease of glucose occurs after a small increment of insulin [3,4], and the normally perfect

relationship between glucose and meals is reduced when the vagus nerve is severed [4]. The implication is that when a rat is going to begin eating, it appropriately anticipates the meal by secreting insulin and lowering its blood glucose, thus helping minimize post-prandial increases of glucose.

Eating impacts many regulated parameters in addition to blood glucose. There are changes of body temperature and metabolic rate, and there may be increased plasma osmolality. Accordingly, when they are monitored continuously, both body temperature [10] and metabolic rate [14,26] have been found to change prior to spontaneous meals in rats; and the changes are such as to minimize meal-induced perturbations while allowing the body to function most efficiently [52]. Animals (and people) consume most water each day in association with meals, a behavioral strategy that will lessen any meal-induced increase of plasma osmolality. The point is that animals make a spectrum of learned responses prior to meals, and these responses collectively help the individual minimize homeostatically disturbing properties of meals.

The ability to anticipate and hence circumvent food-induced changes to regulated parameters is especially important when an individual's lifestyle dictates that daily food intake must be constrained to one or two meals per day. In this instance, the size of each meal must be large if body weight is to be maintained. As a result, the prandial excursions of glucose and other parameters would be abnormally great were it not for the capacity to make meal preparatory responses. Rats prefer to consume their daily food in 10–15 meals per day. They can adapt to eating fewer and larger meals, but the process of adaptation requires several days to become complete, presumably as the animals learn to cope with the impact of the ingested food [7–9]. Animals who cannot make meal-related cephalic responses eat numerous very small meals each day [19] and cannot tolerate large meals [1,15,21,37,45].

An important principle from this discussion is that animals (at least rats and humans) are flexible with regard to the meal patterning they can endure. Ideally, food is freely available and they can eat whenever they wish with no associated cost of procurement. In this situation, they eat a large number of small meals each day. However, if their environment places constraints on eating (e.g. such as predators, demanding social situations, competitors for the same food source, limited periods of food availability, and so on), they can adapt and maintain energy stores by eating fewer and larger meals [7–9]. But this can only happen when the onset of the meals is predictable. If the environment is not regular, or if the adaptive responses are prevented from occurring, animals cannot tolerate large meals [46]. Learning, and predominantly Pavlovian conditioning, is the underlying mechanism for these phenomena.

#### 4. The impact of drugs on regulatory systems

Drugs, as they enter the body and interact with its tissues and molecules, have multiple effects. Some drugs, for example, interact with specific receptors on the surface of cells and thereby mimic and/or interfere with the ongoing effects of endogenous ligands for the same receptors. In this way, exogenous morphine binds to specific opioid receptors on neurons (and other cell types) and elicits reduced pain sensitivity analogously to the way that endorphins and other endogenous opioids bind to the same receptors. Likewise, ethanol is believed to alter cell membrane fluidity as well as interact with receptor-mediated mechanisms. The effects of exogenous drugs that bind to membrane receptors are therefore similar in many ways to the effects of endogenous hormones and neurotransmitters, with the exception that drug effects might be elicited in unusual ways or combinations. Drugs might also, of course, interact with intracellular receptor systems, thus mimicking the effects of certain other classes of endogenous signals (such as steroid hormones, or second messenger systems). The important point is that drugs can cause effects that interact with ongoing neural regulatory mechanisms.

Drugs need not bind to specific receptors to create drug effects. A drug might, for example, directly interact with enzymatic or metabolic processes of cells. Caffeine, for instance, inhibits the actions of the enzyme phosphodiesterase, which normally functions to remove the second messenger cyclic-AMP rapidly once it is formed. Hence, in the presence of caffeine, processes that are driven by c-AMP become amplified and/or prolonged. As another example, cocaine (in addition to other actions) interferes with the reuptake of the neurotransmitter dopamine by neurons. Hence, when endogenous dopamine is released, its functional half-life in the vicinity of synapses (and dopamine receptors) is prolonged. Cocaine administration is therefore associated with enhanced dopaminergic activity. The drug 2-deoxy-D-glucose (2-DG) mimics some activities of endogenous glucose (a natural source of energy for many cells) in that cell-membrane glucose transporters remove it from the extracellular fluid and transport it into cells. However, within the cell 2-DG can not be metabolized within the mitochondria, and it blocks glucose from entering into its normal enzymatic pathway. Hence, 2-DG administration is characterized by a cellular glucopenia. The point is that drugs can alter normal physiology in myriad ways, and most drugs probably work in many different ways simultaneously to produce what are generally known as drug effects (see Ref. [29]).

Therefore, drugs and food share the common property of altering parameters that the body normally monitors and controls. And analogously to those cre-

ated by meals, the perturbations to these regulated parameters caused by drugs can be predicted and consequently minimized or prevented altogether via learned anticipatory responses. Considerable research has been conducted in which individuals given repeated drug administrations become tolerant to the drug. A general conclusion from that literature is that a Pavlovian conditioning model best accounts for many of the data (reviewed in Refs. [32,33]).

Experimental drug administrations are typically associated with a specific environment (e.g. the lab, or the time of day) and a specific administration ritual (e.g. injection). These environmental cues can serve as conditioned stimuli (CSs) which reliably predict the onset of a drug effect. If that drug effect elicits a neural response (i.e. an unconditioned response or UR), the stage is set for Pavlovian conditioning to occur. In this instance, the perceived disturbance of the regulated parameter caused primarily by the drug effect itself is the unconditioned stimulus (US). After repeated pairings of the CS and the drug effect-elicited UR, a conditioned response (CR) can be elicited by the CS in the absence of the drug [12,29]. As an example, if a drug caused body temperature to decrease, the hypothermia (drug effect) would be the US and the neural reflexes that were activated to increase body temperature would be the UR. After several pairings, the CS would elicit a CR (activation of the same neural pathways) and body temperature would increase.

Many of the predictions of such a conditioning model have been verified experimentally in animals using several classes of drugs [33]. Animals that have become tolerant through a conditioning mechanism are thought to receive the full drug effect, but it is countered and hence compromised by the simultaneous elicitation of an organismically generated compensatory response. Therefore, when an otherwise tolerant animal is administered the drug surreptitiously (i.e. in the absence of any drug predictive stimulus or CS), it experiences only the full drug effect and does not appear tolerant [34]. Conversely, if the same animal is presented with the drug-predictive CS, but is administered a placebo rather than the actual drug, the elicited CR occurs in the absence of a competing drug effect, and the effect is analogous to rebound or withdrawal [33].

To cite a concrete example, ethanol is a drug that causes hypothermia. When ethanol is repeatedly administered to an individual in the presence of one set of stimuli, the drug-conditioning model would state that those stimuli would develop the ability to elicit a hyperthermic response by the individual. Thus, when ethanol is administered in the presence of the usual stimuli, the ethanol-induced hypothermic effect is countered and hence neutralized by the conditioned hyperthermic response, and the result is a lessened drug effect or 'drug

tolerance.' Tolerance to the hypothermic effect of ethanol has indeed been found to be consistent with this model [20,23].

In a creative series of experiments, Mansfield and Cunningham associated one stimulus with ethanol administration in rats and a second stimulus with a placebo administration in the same rats [23]. These associations occurred over many trials on which either ethanol or the placebo were given. Eventually, the rats became tolerant to the ethanol-induced hypothermia on ethanol trials, and had little or no thermic change on placebo trials. Some of the rats were then presented with the stimulus always previously associated with the placebo, but administered ethanol instead. In this situation, the rats evinced a hypothermic drug effect and appeared intolerant even though they had been completely tolerant to the same dose of ethanol on a previous trial. Tolerance could therefore be manifest or not depending upon whether or not the animals could correctly predict that ethanol would be given. When stimuli in the environment signaled that ethanol (and its associated hypothermia) was forthcoming, the rats were tolerant. When stimuli signaled that ethanol would not be administered (i.e. when confronted with the stimulus situation always previously associated with placebo administration), the same rats were not tolerant. Hence, tolerance to ethanol-induced hypothermia is stimulus-situation specific. This phenomenon implies that having received a drug repeatedly is, in and of itself, insufficient to cause tolerance to that drug. Rather, an environmental stimulus, one that reliably predicts the drug effect, is necessary for tolerance to be apparent.

In the same experiment [23], if the tolerant rats were presented with the stimulus that predicted that ethanol was forthcoming, but were administered the placebo instead, they increased their body temperature. The implication of this is that the animals, anticipating receiving a drug that would otherwise result in hypothermia, recruited hyperthermic responses. The existence of such a drug-anticipatory response implies that when a tolerant individual is administered ethanol, two processes occur simultaneously. An ethanol-induced hypothermia is offset or countered by an organismically-induced hyperthermia. The net result of the two ongoing processes is little change of body temperature, and the individual is said to be tolerant (see Ref. [29]).

It should be noted that a conditioned hyperthermic response can develop under other circumstances that do not involve drug administration. If rats are placed into a cold environment each day, always in association with a particular stimulus, they develop a hyperthermic response to the presentation of that stimulus [39,42]. What is common to the cold environment and the administration of ethanol is a loss of body heat. In both instances the animal learns, if reliable predictive stimuli

are present, to anticipate the hypothermia and to activate hyperthermic responses. The key aspect is the similarity of the US between the two situations, the perturbation of a homeostatically controlled parameter (body temperature in this example), not the presence or absence of a particular drug.

Ethanol of course has many effects on the body in addition to reducing body temperature. As one example, it causes motor impairment or discoordination. We investigated this phenomenon in rats. Subjects were initially trained to walk on a slowly moving treadmill for 60 s each trial. Any error, defined as stepping off the moving treadmill belt, was automatically recorded and summated. The rats were trained until they essentially made zero error out of a possible 60 s. If these trained rats were then administered ethanol prior to walking on the treadmill, there was a dose-dependent increase of errors. If sufficient ethanol were administered to preclude walking, an animal could achieve 60 s of error. When an intermediate dose of ethanol was administered, an error rate of 30–40 s was observed. If the rats were then given that dose of ethanol every other day for 11 trials, they became tolerant to the ethanol in that they could walk on the treadmill in the drugged state and make very few errors (less than 10 s). Hence, tolerance develops to the motor disruptive effect of ethanol, and rats rendered tolerant to this effect of ethanol comprise the experimental group in the experiments described below [40].

In those experiments, other rats (controls) were administered a placebo each trial (which never caused significant error), or else received ethanol on the same days as experimental rats, but at a different time of the day than when they had their trial on the treadmill (pharmacological exposure group). Hence, these animals were exposed to the same amount of ethanol, and had the same amount of treadmill experience, but were never allowed to walk on the treadmill while in the drugged state. Once tolerance was apparent in the experimental rats, rats in all three groups were given ethanol and given a trial on the treadmill. Control rats, which had never previously experienced ethanol, averaged around 40 s of error. Experimental rats had less than 10 s of error. Rats in the pharmacological group which had previously received the same amount of ethanol as experimental rats, but never in association with a treadmill trial, were intolerant (around 40 s of error) [40,43,44]. Hence, as occurred with the thermic effects of ethanol, having received the drug repeatedly was not sufficient for tolerance to develop. Rather, a specific association is necessary. In this instance, the association is between the drug effect and the treadmill experience.

Although treadmill walking is clearly an operant response and we have previously discussed these findings in the context of an instrumental learning

paradigm [29], the findings of this experiment can also be considered in Pavlovian conditioning terms. If motor discoordination is considered a US, any corrective adjustments to the motor control system might be considered a UR. In this schema, walking on the treadmill, or the moving treadmill itself, is the CS. Hence, the tolerant rats in the experimental group, when placed on the treadmill, make a CR, improved motor coordination in the presence of ethanol, and they make very little error.

In a test of this model [39,42], naive rats were trained to walk on the treadmill. We then confined one group of animals (experimental group) in a small cylinder and spun it rapidly on a platform for several minutes. Immediately afterwards, the rats were placed onto the treadmill for 60 s, and they made around 30 s of error. Over a course of 10 trials spaced every other day, the rats became 'tolerant' to this procedure and made only around 15 s of error after being spun. Control rats were similarly confined but not spun on each trial, and they always made less than 5 s of error. Rats in the treatment exposure group were spun every other day, but never before their practice on the treadmill, and they consequently made very little error (< 5 s). Once the experimental rats were tolerant, rats in the other two groups were spun before being placed on the treadmill, and both control and treatment-exposure rats made significantly more error than experimental rats. Hence, as occurs with ethanol administration, being spun rapidly caused motor discoordination which could be assessed on the treadmill; and, as occurred when ethanol was the causal agent, development of tolerance required the repeated association of motor discoordination plus experience on the treadmill.

In a follow-up experiment [39,42], comparable rats in all three conditions were administered ethanol for the first time. One hour later they were confined but not spun and then placed on the treadmill. Rats in the experimental group made significantly less (around 25 s) error than rats in the control of treatment exposure groups (each around 40 s). Rats which were tolerant to the motor disordinating effect of being spun were therefore 'cross tolerant' to the motor disordinating effect of ethanol.

Cross tolerance between two drugs exists to the extent that an individual who is tolerant to one drug is also tolerant to a second drug, one which has never previously been experienced [41]. A key requirement for cross tolerance to be manifest is an ability on the part of the individual to predict accurately when the effects of its usual (habitual) drug will occur. Hence, when similar environmental stimuli are presented the individual (such as a syringe) and a second, novel drug is administered, its effects can be ameliorated by the conditioned responses elicited by the stimuli. Cross tolerance exists between drugs, or between a drug and some specific environmental situation, by virtue of the

fact that the two cause overlapping regulatory perturbations. This is a key point. In the described experiment, this phenomenon enables the animal to generalize a learned ability to negotiate the treadmill after being spun to a second situation, one where performance would otherwise be ethanol-impaired. Analogously, and as discussed above, rats anticipating being placed in a cold room make a conditioned hyperthermic response. If administered ethanol for the first time and then presented with the CS indicating placement in the cold room, they become less hypothermic than control rats. Again, they appear cross tolerant to the ethanol-induced hypothermia in spite of the fact that they have never previously experienced any drug. In every instance of cross tolerance between drugs, an individual is found to be tolerant to a drug it has never previously experienced. The finding that rats are cross tolerant to a drug after experiencing similar regulatory disturbances expands the scope of cross tolerance by demonstrating that one can become 'tolerant' to a drug without having ever experienced any drug at all.

Therefore, one conclusion that can be reached from these experiments is that drugs are neither necessary nor sufficient to confer tolerance. Rather, what is necessary is a repeated association of activation of a regulatory neural reflex (UR) with an environmental event (CS). Drugs are important because their effects so readily interact with ongoing, regulated systems. Further, there are often environmental stimuli that are reliably associated with their administration. Hence, tolerance often develops rapidly and is manifest as a need to take more drug to achieve a drug effect comparable to what occurred after the initial drug administration. However, comparable conditioning can and does occur when neurally regulated circuits are activated by other (non-drug) experiences.

## 5. Important differences between food intake and chronic drug use

Learning is a powerful and generic strategy that allows animals to respond to anticipated events. Anticipation of an impending disturbance to a regulated parameter allows an animal to minimize that perturbation via activation of learned responses [11,28,29,31,35,38]. Hence, having this ability facilitates homeostasis, a term which encompasses the overall process whereby animals actively attempt to maintain critical bodily parameters within an optimal range [6]. Ingestion presents necessary but predictable challenges to homeostasis, and learning is an efficient means of protecting key bodily parameters in the process. Learning additionally allows an individual considerable flexibility in terms of meal patterns that can be tolerated and hence lifestyle that can be enjoyed.

Like the ingestion of food, chronic drug taking often presents predictable challenges to regulated variables, and these in turn automatically recruit and utilize the same mechanisms that help cope with food ingestion. We believe that the development of behavioral tolerance to a drug is therefore an unavoidable consequence of being able to learn anticipatory responses to homeostatic perturbations. Indeed, the similar role that learning plays in chronic drug use and ingestion has been highlighted in this review. We further believe that learning plays an important role in the drug addiction process [29], and that there are parallels to this addictive process in eating [46]. For example, a drug-addicted individual expecting a drug administration but receiving a placebo may experience a withdrawal-like rebound effect. Likewise, an individual expecting to become hyperglycemic from a sugar-containing food, but who is then unable to consume it, can experience a reactive hypoglycemia [46]. In addition to these similarities, there are important differences between eating and chronic drug use.

Evolutionary pressures have shaped ingestion and its consequences. Reliance upon conditioning processes to circumvent potential negative side effects of ingestion can therefore be considered an optimal strategy. In contrast, drugs are novel in an evolutionary sense, and they cause effects and activate reflexive responses out of an evolutionary context. Further, if conditions permit, these responses can become conditioned. An important characteristic of the conditioning process is that once acquired, conditioned responses may play a role in motivating or at least facilitating repeated experience with the food or drug. This could occur by reducing drug-elicited disturbances via tolerance development as well as through reducing withdrawal-like rebound effects by consuming a food or taking a drug. While the regular ingestion of food is a critical aspect of survival, chronic drug use is not. Furthermore, drugs typically have a greater chance of being toxic than do foods. In addition, of course, the social costs and consequences associated with food consumption are quite different from those of obtaining and using illicit drugs. While in some cases, drug conditioning may benefit an animal by diminishing the intensity of some drug effects via tolerance, it may also contribute to the undesirable consequences associated with drug addiction.

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