PHYSIOLOGICAL AND PHARMACOLOGICAL ASPECTS OF THE CONTROL OF HUNGER AND THIRST

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TABLE OF CONTENTS

INTRODUCTION

Hunger and thirst are sensations of a general character which are difficult subjects for a scientific analysis. Most of the older literature on these subjects deals with more or less introspectively coloured studies in man. However, concomitantly with the development of new methods of study in unanaesthetized animals more and more information on the physiology of the urges to eat and drink has been gained. Our present knowledge of these mechanisms is thus a synthesis of the results of studies both in man and in animals. In general it has been stated that many factors concerning the regulation of food and water intake are known, but these are far from completely understood.

Prior to this century, three theories, still of some current interest, were advanced to explain the sensation of hunger. One suggested that hunger was of peripheral origin. Another theory claimed that hunger was a general sensation, and finally a third theory considered hunger to be of central origin. The first theory claimed that stimulation of afferent nerves in general, evoked by some changes in all tissues, or of a more strictly localized group of afferents, mainly in the stomach, should result in hunger (48). Since it could be shown (26) that the feelings of hunger pangs coincide with particular hunger contractions in the empty stomach, these contractions were considered to be the condition eliciting the sensation of hunger. Hypoglycemia was found to strengthen hunger contractions whereas the injection of glucose was shown to have a depressing effect (25).

The theory that stomach contractions play a dominant role in hunger has been made somewhat dubious since it has been shown that total denervation or the operative removal of the stomach has no dominant influence on the regulation of food intake (46, 97). On the other hand, the theory that there is a hunger "centre" in the brain, sensitive to a starvation state of the blood (69, 77) has in recent years received strong experimental support and is presently the commonly accepted explanation of hunger.

Several different theories have also from time to time been formulated to explain the sensation of thirst. All these theories are discussed and practically all literature of any scientific value on the subject, published up to 1958, is extensively reviewed in Wolf's excellent monograph, "Thirst" (115).

LEVELS OF CENTRAL CONTROL OF HUNGER AND THIRST

A. Hypothalamic "centres" for food and water intake

The importance of the hypothalamus for the regulation of food and water intake has been demonstrated mainly through ablation and stimulation experiments. Various species of experimental animal from birds (15, 36) to monkeys (5) have been used for these studies. In general the results are consistent in indicating the lateral hypothalamus as the site of a "hunger centre," whereas the ventromedial part seemingly takes part in reactions of satiety. An area located medial to, and extending somewhat rostral to the "hunger centre" seems to be concerned with the regulation of water intake.

Thus, with regard to the regulation of food intake it has been shown that lesions involving the lateral parts of the hypothalamus may cause either temporary or permanent aphagia (1, 5, 80, 105). Lesions involving the ventromedial nuclei have the opposite effect, causing overeating and obesity (22, 51, 52). As could be expected from the results obtained by lesions, electrical stimulation within the lateral hypothalamus may in unanaesthetized animals be seen to cause hyperphagia (3, 15, 24, 30, 63), whereas stimulation in the ventromedial hypothalamus may induce what seems to be satiety (88).

Evidence that the hypothalamus is involved also in the regulation of water intake is the observation that local injections of small amounts of hypertonic saline within an area of the hypothalamus located close to the third ventricle may induce polydipsia in the goat (6, 7, 10). In the same animal drinking may also be induced by electrical stimulation within a region having its centre in the middle of the hypothalamus between the descending tract of the fornix and the mammillothalamic tract (11). Stimulation experiments in the rat (44) and the dog (8) indicate that a "drinking centre" is located in the same place in these species, whereas in birds structures taking part in the regulation of water intake may be located slightly more rostrally in the medial parts of the preoptic area (15).

The results of lesion experiments performed to localize a "drinking centre" in the hypothalamus are somewhat less consistent than are those of stimulation experiments. It has been shown that lesions in the lateral hypothalamus of rats (78, 81, 100) reduce or even abolish drinking, which has been taken as an

indication that the "hunger" and "thirst centres" are anatomically very closely linked together. A detailed anatomical analysis of the extent of lesions in the lateral hypothalamus of rats, causing both adipsia and aphagia, has revealed that the common denominator for all these lesions seems to be damage to the medial forebrain bundle (81). This observation has led to the suggestion that the medial forebrain bundle may be as important as the lateral hypothalamus proper in the control of food and water intake. The results of hypothalamic lesions made in dogs (12, 113), however, like these of stimulation experiments, strongly indicate that the urges to eat and to drink originate from different areas of the hypothalamus. Thus, dogs made temporarily or even permanently adipsic by hypothalamic lesions may well retain their urge to eat. The inconsistency of the results of ablation studies may therefore tentatively be explained on the assumption that the urges to eat and to drink emanate from two anatomically separated parts of the hypothalamus but that these urges are propagated to a higher level of the central nervous system by way of the medial forebrain bundle. This assumption is supported by the observation that extensive lesions in the preoptic area affecting the medial forebrain bundle may interfere with the normal urges to eat and drink (8).

B. The importance of other parts of the central nervous system for the regulation of food and water intake

Medullary reflexes are obviously essential for normal feeding and drinking. Some evidence that bulbar mechanisms may also be of importance for the development of the urge to eat has been presented. Electrical stimulation in the vicinity of the dorsal motor nucleus of the vagus may thus produce indiscriminate hyperphagia in the sheep (63). Further work is needed, however, to elucidate the eventual importance of medullary mechanisms for the development of hunger and thirst.

Some additional evidence for the localization of a thirst mechanism outside the hypothalamus has been produced by the observation that lesions involving the subcommissural organ may cause adipsia in rats. The interpretation of this finding is obscured by the observation that injection of extracts of this organ caused a reduction in the water intake (42). Attempts to obtain a similar effect by extensive damage to the subcommissural organ in the dog were not successful (8).

The importance of "higher centres" for the regulation of food intake has been studied in different animals (2, 4, 31). Frontal lobe lesions including or restricted to the posterior orbital cortex in the monkey and the cat lead to a decreased food intake, whereas extensive temporal lobe lesions are followed by an increase in food intake, preceded by an initial decrease if the amygdalae also are involved. Such changes are more marked in monkeys than in cats but are not so pronounced as those associated with lesions of the hypothalamus. It is concluded that frontal and temporal lobe structures modify food intake through a discriminating mechanism (appetite) which is better developed in more highly encephalized animals. This appetite mechanism may influence the primitive urge (hunger) originating at the hypothalamic levels (4).

EVIDENCE THAT HYPOTHALAMIC STIMULATION MAY ELICIT TRUE HUNGER AND THIRST

It is obviously not justified to conclude that eating and drinking induced by hypothalamic stimulation are by themselves reliable indices of hunger and thirst. It has been pointed out by Miller (75) that if one is interested in the broader aspects of hunger and thirst as drives to motivate behavior, it is not safe to rely solely on measures of food and water intake. For example, it has been found that rats made hyperphagic by lesions in the ventromedial hypothalamus show a decreased satiety but no increased hunger as measured by their willingness to work for their food or to eat food of an unpleasant taste (76). Electrical stimulation in the lateral hypothalamus seems, however, to have the same general properties as normal hunger in that it will elicit not only eating but also the performance of learned food-seeking responses in the satiated animal (75, 116). These observations support the assumption that the lateral hypothalamus is the site of a hunger mechanism whereas the ventromedial area contains a satiety mechanism (1).

Similar evidence has been produced to show that hypothalamic stimulation causing drinking elicits a sensation of thirst. Electrical stimulation of the hypothalamic "drinking centre" in goats may thus elicit a conditioned motor reaction originally developed on the basis of normal thirst (13). Stimulations of this "centre" may also induce goats to solve simple problems in order to get access to water (16).

FACTORS OF IMPORTANCE IN ELICITING HUNGER AND THIRST

A. Hunger

As mentioned previously, it has been generally concluded that food and water intake are centrally regulated mechanisms. Animals in which electrical stimulation of the lateral parts of the hypothalamus will cause an increase in food intake stop eating when lesions are placed bilaterally in the same area. Lesions in the ventromedial area of the hypothalamus will produce obesity due to overeating. These findings suggest the existence of a "feeding centre" in the diencephalon with its lateral part exerting the more basic type of food intake control (the "hunger centre") which is partly regulated by the medial component (the "satiety centre") (20).

Thus far the nature of the adequate feeding stimulus is not known. As a result of the last ten years of research on this problem it is becoming more and more obvious that the adequate stimulus for the "feeding centre" is of multiple origin. The importance of heat production, more specifically the specific dynamic action of food, has been suggested as one factor regulating food intake (19). This means that the heat content of the body will influence the "feeding centre." In this connection it is of interest to note that the hypothalamus also is concerned with the regulation of body temperature (70). As pointed out by Brobeck (20) there is strong evidence that the hypothalamus integrates these functions so that changes in the functional level of the regulators influence one another.

A theory of a glucostatic mechanism regulating food intake has been introduced (73). The theory is based upon certain experimental findings both in man and in animals. From measurements of the difference in glucose concentration between carotid and jugular blood, it has been found that when this value approaches zero the sensation of hunger appears—an observation which has led Mayer (73) to suggest that certain parts of the hypothalamic "feeding centre" may contain "glucoreceptors." Since the ventromedial area of the hypothalamus is concerned with satiety and seemingly acts as a brake on the otherwise more or less constantly activated lateral parts (the "hunger centre"), Brobeck (20) suggested that what is regulated should not be hunger but rather satiety. Additional support for this hypothesis is given by the observation that gold thioglucose which, when injected into mice produces obesity, causes lesions mainly concerned with the ventromedial parts of the hypothalamus (72). It therefore seems possible that if "glucoreceptors" exist in the hypothalamus they ought to be located in the ventromedial area (the "satiety centre"). According to Mayer (73) it is not the absolute values of blood glucose which may stimulate the postulated "glucoreceptors" but the rate of glucose utilisation. In this respect the arterio-venous difference has been taken as an index.

Adjustments of feeding may also be made in relation to the amount of stored fat in the body (60). The control areas of the hypothalamus should thus be sensitive to the concentration of some metabolite in equilibrium with the stored fat. Studies in parabiotic rats support this theory. It has been shown that if one of the connected rats is made obese by ablation of the ventromedial "satiety centre" its partner will lose weight due to a decreased food intake (50).

It is interesting in this connection to note that measurements of the uptake of labelled phosphorus in different areas of the hypothalamus in hungry and fed mice show that there is an increased biochemical activity in the "feeding centre" during the hungry state (40, 41).

In summarising the question as to the adequate physiological stimulus for the regulation of food intake it should again be pointed out that conclusive evidence for one of the factors mentioned above as the sole regulator is missing. Rather, one gets the impression on the basis of the experimental data that all are of some importance, and, furthermore, the possibility of important undiscovered factors cannot be dismissed.

B. Thirst

Since a negative water balance is the condition most often associated with thirst, dehydration would logically be expected to be the crucial factor eliciting it. But dehydration means a number of changes in the condition of the body fluids, any or all of which could be factors eliciting thirst. Water deprivation results in a decrease in extracellular fluid volume, a decrease in intracellular fluid volume, and an increased tonicity in both these fluid compartments. All of these changes have also been observed in association with thirst. But thirst is also elicited by the injection of solutions of sodium salts, which cause no absolute dehydration but a movement of water from the intracellular to the extracellular

fluid compartment and a rise in the tonicity of both compartments. The rise in body fluid tonicity *per se* does not seem to be the cause of thirst. An increased tonicity due to the injection of urea, which unlike sodium salts freely moves into the intracellular fluid compartment and therefore causes no net movement of water, is much less effective in producing thirst than an equivalent rise in tonicity due to the injection of hypertonic saline (43). The main factor in common during the state of dehydration and during thirst is thus a decreased intracellular fluid volume, speaking in favour of "cellular dehydration" as the crucial factor in thirst. The same factor has, in refined experiments on the unanaesthetized dog, been shown to cause the release of antidiuretic hormone from the neurohypophysis, a release which is mediated by "osmoreceptors" located in the anterior hypothalamus (109, 110). It is therefore not unreasonable to suggest that the urge to drink may originate from similar "osmoreceptors," perhaps located in the same part of the brain stem. Evidence in favour of this idea has been produced by an osmometric analysis of thirst in man and in the dog showing a 1 to 3% change in cellular water content at the "threshold of thirst" (114), which agrees favourably with the 1 to 2% change reported to be necessary for the activation of the hypothalamic "osmoreceptors" causing the release of antidiuretic hormone (109). Additional evidence that hypothalamic "osmoreceptors" are concerned not only with the release of antidiuretic hormone but also with the development of an urge to drink has been produced by the observation that the direct injection of minute amounts of hypertonic saline into a specific area of the hypothalamus of the goat may elicit polydipsia (6, 10). Conversely, it has been observed that injections of minute amounts of distilled water into the third ventricle of moderately thirsty cats decreased water consumption and reduced the rate at which the animals would perform a learned response rewarded by water (75). Furthermore, the threshold for eliciting drinking by electrical stimulation of the "drinking centre" has been found to increase during the hydrated state (14). Recordings of the electrical activity of single neurons in lightly anaesthetized animals have further directly demonstrated the presence of osmosensitive cells in the anterior hypothalamus (28).

Studies which employed electrical recording within the brain have indicated that osmosensitive elements are located not only in the hypothalamus but also in the olfactory bulbs (103) and in the area postrema of the medulla (27). Whether these extrahypothalamic osmosensitive areas of the brain are involved in the thirst mechanism is not known. It has, however, recently been demonstrated (104) in animals in which the hypothalamus was isolated from the rest of the brain that whatever role osmosensitive elements in the rest of the brain may play, there are, as Verney proposed (109), receptors in the diencephalon capable of activating the neurohypophysis in response to hyperosmotic stimuli.

However, cellular dehydration is apparently not the sole factor eliciting the sensation of thirst. It has been shown that salt-depleted animals having an increased intracellular fluid volume may show increased drinking as compared to the period before salt depletion (54, 55). Thirst may thus exist in the absence of cellular dehydration. To explain this phenomenon a theory has been proposed

(86, 114) that any change in the "osmoreceptor" cell volume above some threshold value would be an effective stimulus for thirst. Another possible explanation would be that even in the state of cellular hydration a decreased extracellular volume may act as a factor eliciting the urge to drink. But the role played by extracellular volume changes in eliciting thirst awaits further experimental elucidation.

RELATIONS BETWEEN FOOD AND WATER INTAKE

The ingestions of food and water are very closely related. In dogs and rats hunger and thirst show a diurnal cycle (93, 98, 118). Two possibilities exist. One possibility is that a diurnal pattern exists for food intake and that water intake passively follows it; the second is that a diurnal pattern exists for both. After eliminating the diurnal cycle in food and water intake, there is still a very close temporal relation between the two in that most of the daily water intake follows within a few hours of eating (45, 85). The amount of intake of food and water are also related. Food consumption is reduced during water deprivation (111) and the same holds true for water consumption during food deprivation (66). The way that food intake affects the fluids of the body has been little studied. It is, however, certain that both "appetite secretions" and secretions of digestive juices due to the presence of food in the alimentary canal cause great quantities of fluid to move into the gastrointestinal tract, reducing extracellular fluid volume by a considerable amount. It can further be assumed that after food ingestion forces are acting to restore the content of the stomach and intestine to isotonicity. If exogenous water is not available, water must be mobilized from the tissues to reduce the concentration of solutes. That this evidently happens has recently been shown by measurements of the electrical conductivity of the body fluids *in vivo*. Such measurements have revealed that food ingestion and digestion cause an increased electrolyte concentration in the extracellular fluid presumably due to the movement of water into the gastrointestinal tract (87). These findings indicate that food intake has temporarily all the effects on water balance as has deprivation of water, and they thus offer an explanation to thirst following upon eating, the so-called postprandial thirst.

FOOD PREFERENCES

In the case of specific hungers there is evidence that food preferences and diet selection depend to a large extent upon changes in the internal environment produced, for example, by pregnancy, dietary deficiencies, endocrine disturbances (91), or obesity (64). In self-selection experiments in nonpregnant, pregnant, and lactating rats it has been found that very marked changes in the preferences and requirements of the animals for different foods and minerals take place (92). There are increased demands for protein and fat during pregnancy and lactation but no change in carbohydrate appetite. This finding has since been confirmed in mice (64). Mice with obesity induced by hypothalamic lesions will behave very much like pregnant and lactating animals in preferring a high fat

diet during the weight-gaining period (64, 65). Since the obesity of these animals is a consequence of lesions in the hypothalamus, the experiments give evidence that the bodily needs not only for carbohydrates but also for other nutritional compounds manifest themselves through the mediation of the hypothalamic mechanism regulating food intake.

In a wider sense, then, the sensation of hunger means more than a manifestation merely of the caloric needs of the organism. It is, for example, well known that herbivorous animals, the normal food of which contains insufficient sodium, show a specific hunger for salt. Adrenalectomy leading to an increased urinary excretion of sodium will cause a similar salt hunger (91). Evidence that a hypothalamic mechanism is involved also in the self-regulation of mineral salt intake is given by the observation that hypothalamic stimulation in the goat may cause what appears to be a rather specific urge to lick a salt block (15).

The results from studies on the selective behaviour in birds towards taste solutions (56, 59) have been confirmed by electrophysiological experiments (61). Behavioural studies show whether an animal will prefer, reject, or discriminate for or against a substance, but they usually will not demonstrate whether that substance actually stimulates chemoreceptors, touch or cold receptors in the tongue, or similar receptors elsewhere in the mouth or on prehensile organs. To obtain that knowledge electrophysiological or anatomical studies have to be added (61).

SATIETY

Satiety has been identified with physiological anorexia, a state of lack of desire to eat (57). As has been pointed out above, certain changes in the internal environment may, by stimulating postulated receptors in the ventromedial "satiety centre" in the hypothalamus, act as a brake on the "hunger centre" and thus induce a state of satiety. The activity of the "feeding centre" as a whole is, however, evidently influenced also from other parts of the brain and from the periphery. It has thus been shown that frontal lobotomy may lead to increased appetite in man (74), and experiments in dogs have demonstrated that the anorectic effect of amphetamine is to a large extent exerted from the prefrontal areas of the cerebral cortex (9, 31). Gastric distension is a factor which evidently also may act reflexly upon the "feeding centre" in the hypothalamus and induce satiety. Food intake in dogs is thus influenced to a large extent by distension of the stomach (58, 96). A neurophysiological basis for the influence of gastric distension on food and water intake has been given by the observation that the frequency of neural response in the vagus is a linear function of the amount of balloon-induced distension in the stomach (89). The influence of gastric distension on food intake is, however, active only on a short-time basis since a chronic distension of the stomach and intestines will result in compensatory hypertrophy (splanchnomegaly) or dilatation. Animals receiving a food which is calorically diluted will thus compensate for this dilution by increased food intake (65).

Satiety for water may not be an adequate expression. A more correct designa-

tion would be physiological adipsia (114). Satiety as contrasted to hunger may be expressed as a desire not to eat. Satiety for water, on the other hand, may not necessarily mean a desire not to drink. This discrepancy may be due to a principal difference in the organisation of the two mechanisms regulating food and water intake. Although food intake seems to be regulated by the balance between a "satiety centre" and a "hunger centre," there is so far no evidence for the existence of a "satiety centre" for water. The removal of a "centre" of this kind would cause excess drinking. Any such effect has not been observed as a consequence to hypothalamic or other central lesions. The polydipsia seen in cases of diabetes insipidus is not to be considered as due primarily to abnormal thirst. It is rather a physiological activation of the thirst mechanism due to preceding abnormal water losses by the urine (38, 53, 90). Thus, as long as no water is needed, the hypothalamic "thirst centre" seems to be in an inactive state. Cortical influences, however, may evidently decrease the excitability of this "centre" and it may seemingly also be inhibited reflexly from the periphery. The "thirst inhibitory" action of amphetamine in the dog is thus markedly diminished after prefrontal lobotomy (9), and at least two factors during the process of drinking have been shown to be of importance for the alleviation of thirst. With unvarying water deficits sham-drinking is not constant in dogs with oesophageal fistulas. If water is allowed at different times after the last drink, the amount of sham-drinking is less for shorter intervals (17). In similarly prepared dogs it has further been shown that approximately 250 % of the water deficit is sham-ingested before temporary satiation is afforded the dogs (107). A pharyngeal factor thus seems to act for temporary alleviation of thirst. Which of the many consequences of water in the mouth and pharynx is important in the satiation effect is not known. It is interesting to note in this connection that specific taste receptors for water have been found in the frog (119) and certain mammals, including the dog and the monkey (67, 120). Whether they are of importance for the temporary alleviation of thirst remains to be elucidated. The stimulation of cold receptors in the mouth and the pharynx may also be a component of the pharyngeal factor (14, 16).

A second factor acts below the oesophagus. A number of studies on dogs has shown that in certain circumstances the mechanical effect of stomach distension can inhibit drinking (54, 79, 107). An almost linear relation between the per cent inhibition of sham-drinking and the extent of stomach balloon inflation seems to exist in the dog (107). Although thus definitely shown to be a component of the satiety mechanism for thirst, the gastric distension factor may have been overestimated. This factor was first postulated because absorption of water seemed too slow to account for the cessation of normal drinking. There is, however, recent evidence to suggest that water ingestion produces systemic fluid changes much more rapidly than would be predicted on the basis of absorption alone (87). It has thus been shown that even during the first period of drinking, which lasts 8 to 10 minutes in dehydrated rats, the conductivity of the extracellular fluid decreases, indicating a lowered concentration of electrolytes. The results were explained by the hypothesis that not only can water

move out of the gastrointestinal tract and into the extracellular fluid, but salts can go in the opposite direction, both along their respective concentration gradients. These movements would cause rapid, temporary amelioration of the osmotic changes while volume would be affected more slowly. Thus, extracellular fluid changes could be produced more quickly than had been previously predicted on the basis of absorption rates alone, suggesting that they play a more important role in the satiation of thirst than has been formerly assigned (87).

PHARMACOLOGICAL ASPECTS OF HUNGER AND THIRST

Variations in food intake are normally followed by similar variations in water intake. Agents affecting the urge to eat, and consequently the food consumption, have therefore also a secondary effect on water ingestion. However, due to the principal differences in the hunger and thirst mechanisms, these urges may also develop quite independently of each other. Under such circumstances factors affecting the one state may not necessarily influence the other. In spite of this fact, the effects of some hormones and drugs on hunger and thirst are here treated together.

A. Stimulating agents

Insulin. Presumably related to hypoglycemia produced by insulin are the reports that insulin increases food intake in the dog (46, 47). It has, however, been found that daily injections of insulin in intact rats do not cause any increase in the growth rate (37). On the other hand, in hypophysectomized rats insulin produces a marked increase in growth rate (94), whereas growth hormone produces this effect whether or not the animals are hypophysectomized (35, 94). On the basis of these conflicting data, no definite conclusions can be drawn as to the influence of insulin on food intake and body weight.

Insulin has also been found to increase water intake independently of its effect on food intake in the rat (86). Since insulin causes water to move out of the extracellular fluid compartment and into the cells (117), cellular dehydration is, in this case, obviously not the cause of the increased urge to drink. Novin (86) suggested two possible explanations for his findings. Either the "osmoreceptors" are unable to discriminate the direction of change in their volume and report any cellular deformation above some threshold value as "thirst," or thirst in these experiments may be the result of a decrease in extracellular fluid volume. It is interesting to note in this connection that Verney (109) has found insulin to affect water metabolism in another way, namely to cause a release of antidiuretic hormone in the dog.

Other hormones. Increased food and water intake has been reported in women on the days immediately preceding menstruation (106). In rats the oestrus cycle markedly influences the food intake, spontaneous activity and the body temperature. Thus at oestrus the desire for food is decreased as well as the body temperature, while the spontaneous activity is increased (23). The results offer an explanation for the opinion that castration often results in obesity. Disturbances in pituitary function have no predominant influence on the de-

velopment of hypothalamic obesity (51). On the other hand, various pituitary hormones seem to influence food preferences. Since the rather contradictory results of studies on the influences of sexual and anterior pituitary hormones on food and water intake have been extensively reviewed recently (99) they are not further discussed here.

Gold thioglucose. About 150 years ago it was reported that corpulence occurred very frequently after the use of mercury in the treatment of syphilis (112). The use of another heavy metal, gold, in the treatment of arthritis caused the observation that LD50 doses of gold thioglucose could produce obesity in mice (18). It was found that the obesity was the consequence of a chronic hyperphagia. Later studies suggested that the compound acts on the hypothalamus by destroying the satiety part of the "feeding centre" (32, 72). It has further been found that fasting prior to the injection of gold thioglucose increases the incidence of obesity. Since BAL (dimercaptopropanol) produces an increase in the survival rate and a concomitant decrease in the incidence of obesity, the brain damage appears to be caused by the action of the heavy metal (32).

Ethyl alcohol. Alcohol may induce thirst in man and increase water intake in experimental animals. This is one of the features of acute alcoholic intoxication as well as the "hang-over" period. It has been observed that alcohol ingestion in man causes a retention of electrolytes leading to an expansion of the extracellular fluid volume (84), and similar observations have been made in experimental animals (68). Furthermore, alcohol has a diuretic effect during the period of rising concentration in the blood, which is at least in part due to an inhibition of the release of antidiuretic hormone from the neurohypophysis (62). Both these effects are likely to cause cellular dehydration which may be the cause of the thirst observed subsequent to the consumption of alcohol (114).

B. Inhibitory agents

An increased food intake over a long period of time will result in obesity which has become a public health problem of great importance, since obesity may either directly or indirectly lead to secondary diseases such as circulatory diseases (71a) or diabetes mellitus (37a, 61a, 71a). Also in experimentally induced obesity, diabetes mellitus has been encountered (64). The reduction of weight will reduce the severeness of the diabetes mellitus in obese cases both in human subjects (48a, 83) and in dogs (64a). In the treatment of obese patients one runs into difficulties of various kinds. Thus, obesity frequently occurs without any clinically visible reasons. In those cases where the cause is unknown the treatment has to be empirical. A common item of advice to the obese is to increase the exercise, *e.g.*, the muscular activity. It has been found that overweight is more common among people with a profession demanding little muscular activity (74a). Furthermore, a restricted diet is usually recommended. It is here the use of appetite-depressing agents has proved to be useful. As a result, many pharmacological studies have been directed towards appetite depressants or anorexigenic agents.

Although not an appetite depressant, thyroxin or extracts of the thyroid have long been used to facilitate weight loss in the obese. This type of treatment, however, has lost much of its importance since it has become obvious that it is much easier to avoid calories than to burn them away (83). Instead, the use of sympathomimetic amines which have an anorexigenic effect has increased in the treatment of overeating (49).

Amphetamine. Subsequent to the observation that this drug has an anorexigenic effect in man (29, 82, 108) numerous reports of the effect of sympathomimetic drugs on food intake have appeared. Such drugs have been found to increase spontaneous activity in experimental animals (95). The anorexigenic effect of amphetamine persists after vagotomy or splanchnolumbar sympathectomy, indicating that the effect is not due to sensations from the gastrointestinal tract. The current opinion as to the mode of action of sympathomimetic drugs in producing anorexia leans toward a central action. Amphetamine has thus been found to change the electrical activity in the ventromedial hypothalamus (the "satiety centre") in cats (21). This finding does not exclude the possibility that the main site of action is located somewhere else in the brain. Evidence that amphetamine has an indirect action on the hypothalamic "feeding centre," mediated by the prefrontal and perhaps other association areas of the cerebral cortex, is suggested by the observation that its anorexigenic effect is markedly reduced by prefrontal lobotomy in the dog (9, 31).

Amphetamine has also been shown to inhibit drinking in dogs and rats (9, 34). This effect does not seem to be a secondary effect of hunger depression, since drinking which would be expected to occur after the intravenous injection of hypertonic saline in the dog is also inhibited. Like the anorexigenic effect, the antidipsic action of amphetamine is at least in part mediated by the prefrontal areas of the cerebral cortex in the dog (9). It seems, however, to involve a depression of the hypothalamic "thirst centre" since the administration of amphetamine to goats inhibits the drinking otherwise seen to persist for some time after discontinuation of prolonged electrical stimulation of this "centre" (16).

Phenmetrazine. In recent years a new drug, phenmetrazine (Preludin), has been introduced as an appetite-depressant agent (35a, 37a, 41a, 89a). Presumably the mode of action of this substance is similar to that of amphetamine (37a). Most clinicians agree that both amphetamine and phenmetrazine are useful agents in the treatment of overweight, provided the patients are under regular control.

Glucagon. The most conspicuous effects of glucagon are a rise in the concentration of blood glucose and an immediate decrease in liver glycogen (39). For this reason it has been used in studies of the hunger and satiety mechanisms (102). Glucagon will inhibit gastric hunger contractions and cause a loss of the subjective sensation of hunger in man. Concomitant with a rise in the blood glucose level there is also an increased glucose difference between carotid and jugular blood (102). Studies of gastric contractions in rats have revealed that neither glucose nor insulin given intravenously affects the fasting contractions. Glucagon, however, invariably produces complete inhibition of these contractions (81a).

CONCLUDING REMARKS

The present review is mainly an attempt to summarize what little is known about the physiology of hunger and thirst. The action of drugs on these drives has consequently been discussed solely in terms of the physiological aspects of their actions. A consideration of drug effects on hunger and thirst in psychological terms has been outside the scope of the present review. More substantial understanding might conceivably be provided by consideration of the psychological aspects of hunger and thirst, since these can be expected to have a significant role in the control of these drives by drugs.

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