Metering of intravenous versus oral nutrients and regulation of energy balance

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The role of substrate availability as a factor controlling feeding can be directly tested by flooding the systemic compartment with metabolizable substances. What would happen to feeding behavior if the total amount of oxidizable substrate furnished to the cells (from all of the above reservoirs) were artifically and continuously infused into the systemic compartment at approximately the ongoing metabolic rate (MR)? Such results, obtained under conditions of complete bypass of extrasystemic sensory mechanisms, can tell us about the integration of sensory information involved in the regulation of energy balance.

At this time we are able to elaborate and extend our preliminary reports (19, 26, 27) and incorporate the results into a novel theoretical model of metering and integration.

EXPERIMENTAL

General Method

Using Nembutal anesthesia (40 mg/kg, ip), male adult Wistar rats (250-400 g) were fitted with indwelling jugular catheters of silicone rubber and a terminal skull fixture (20). Powdered food (Extralabo M25: calorlc yield 3.2 kcal/g corrected for fecal loss, or a semisynthetic diet T-Amidon: 3.8 kcal/g) and water were available ad libitum. The rats were individually housed in cylindrical Plexiglas cages maintained in a 12:12 lighting cycle. During infusions the rats were permanently connected to a pump-driven syringe via polyethylene tubing and a watertight swivel (20). Daily weighing of rats (+ 2 g) and intakes (+ 0.1 g) was carried out in the 2nd h of the light period (0900-1000).

After 3-5 days of postoperative recovery, a control infusion of 0.9% NaCl was given for 2-3 days, during which time intakes were invariably stable and not different from the uninfused food consumption. The mean oral food intake (OFI) during this period was thus used as a measure of the steady caloric requirements of the individual in a state of balance and is referred to as 100% base-line (100 BL) need.

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The period of control infusion was followed by a series of nutritive infusions. The rates varied from 20 to 120 ml/24 h and for 2-50 days. The rate of infusion was constant unless otherwise mentioned. The residual OFI was measured, and averages were computed both within and between animals for comparable infusion parameters. Urinary losses were not considered in the

intravenous infusion; feeding; ischymetric; insulin; specific appetite
calculations, since these were expected to be similar in both control and nutritive infusion conditions; glycosuria was never observed (Clinistix spot checks on collected urine). In some cases the patterns of OF1 were recorded on chart paper using a continuously weighing strain-gauge device. Meal size and intermeal intervals were calculated (15) using a 20-min flanking definition of a meal.

The infusion technique allows complete liberty of movement and allows the unstressed animals to sleep in normal posture (head tucked under body) (20); the experiments were terminated at the first signs of sickness or distress.

Experiment 1

Forty rats served in this experiment in which the intravenous infusions were designed to supply a known fraction (range 50–140%) of the daily energy requirements (100 BL). The fluids infused were pure glucose or mixtures including amino acids and oligoelements shown in Table 1. Each infusion (rate and composition) was given until at least two consecutive days with no further change in OF1 had passed; most rats were infused for considerably longer than this minimum period. The reduction in OF1 from 100 BL was calculated in kilocalories and divided by the energy infused per 24 h to yield the reduction ratio (RR)

\[
RR = \frac{\text{control OF1 (100 BL)} - \text{OF1 during infusion X}}{\text{infusion X}}
\]

which is hence a measure of the efficiency with which the infusion decreased OF1. The RR was calculated separately as a function both of infusion rate and of fluid composition.

An additional three rats were fed a cellulose-diluted diet (5 parts M25 chow: 4 parts cellulose flour: 1 part kaolin wt/wt, plus saccharin 0.1% flavoring) with a calorific value of 1.8 kcal/g. The animals were offered this diet for several days and then undiluted M25 for a similar period with the same intravenous infusion throughout.

Experiment 2

Eleven rats received an infusion of regular insulin (Actrapide, Novo) in parallel with the principal intravenous infusion of glucose or saline control. The principal infusion rate (20–80 ml/24 h) and concentration (20–30% glucose in water) were held constant for 2–5 days until stable intakes were observed. Each rat served as its own control (saline infusion) as well as in as many nutritive conditions as possible. The infused fluids were maintained separately until passing through a double-lumen swivel and Y-piece at the rat’s head (20). In all cases the mean RR was calculated as above.

Experiment 3

Discontinuous intravenous infusions were administered to eight rats. The intravenous nutritive fluid was in all cases a 3:1 vol/vol mixture of 30% glucose and L-Trophysan (a commercially available amino acid solution; see Table 1) yielding 1.1 kcal/ml. The infusions were programmed to simulate normal feeding patterns. This was accomplished by detecting the spontaneous meals of an uninfused “leader” rat and using these signals to trigger a timed intravenous infusion for the experimental rat. The infusion rate was 0.13 or 0.20 ml/min, and the duration of the infusion was timed at 10–30 min. The minimum duration (10 min) was thus about the length of meals of the leader rat, whereas the 30-min infusions outlasted the spontaneous meal. The maximum infusion was 6 kcal, or the equivalent of about 2 g of chow—a normal meal size. Every animal served in a control phase when identical discontinuous 0.9% NaCl infusions were programmed. The 100 BL and RR were calculated as before.

RESULTS

Experiment 1

Infusions of the nutritionally adequate fluids shown in Table 1 led to reductions of OF1. When the results from all healthy animals were considered for these solutions, it was found that the magnitude of the OF1 reduction was correlated with the amount infused \((r = 0.63, df = 28, P < .01)\) within the range studied. The mean slope of the regression \((\text{RR})\) was 0.64, indicating a less than calorie-for-calorie reduction of OF1.

Effect of infusion composition of OF1. The RR was calculated separately for each fluid (Table 2). The lowest RR was observed with glucose, whereas diets that were more nutritionally complete led to higher RR values. The mixture of glucose and Trophysan yielded the maximum RR (liquid 5 in Tables 1 and 2). Additional experiments (26; unpublished observations) have revealed that infusions of pure amino acids or of the commercial preparations (Trophysan, Aminosol) alone are without effect on OF1 in the short or long term. Infusions of sorbitol, the principal constituent of

| Table 1. Composition of most successful intravenous nutritive fluids |
|--------------------------|-------------------|-------------------|
|                        | Solution 5         | Solution 6         |
|                        | 2                 | 5                 | 6                 |
|                        | g/liter           |                  |
| Seven amino acids      | 5.45 (L)          | 12.65 (DL)        | 5.45 (L)          |
| Arginine               | 7.22              | 0.50              | 7.22              |
| Methionine             | 1.10              | 2.20              | 1.10              |
| Glycine                | 24.0              | 25.0              | 24.0              |
| Salts                  |                  | +                 |                  |
| Vitamins               |                  | +                 | ++                |
| Glucose                | 580               | 150               |                  |
| Sorbitol               | 49                | 290               |                  |
| kcal/liter             | 2,500             | 1,000             | 1,500             |

Solution 5 is a mixture of Trophysan and 30% glucose (1:1); initially the amino acids (isoleucine, leucine, lysine, phenylalanine, threonine, tryptophan, and valine) were infused, but in later formula the same N content was from pure L-amino acids (24). Salts included Co, Mn, K, Na, Cl, HCO3, and the vitamins B6, B12, Ca, pantothenate, and ascorbic acid. +, the presence of some of these trace elements; ++, most or all present.
The mean residual OF1 of rats in this group was 30% body weight change was greatest on the 1st day of the infusion group, n = 13, showed stable body weight (mean 100 BL infusion, probably due to net shifts in fluid balance. This fraction is greater for fluid 2 than 5 (P < .05, U test on body weight changes).

The intravenous and total (intravenous plus oral) mean intake is shown (+ SE) as % BL (saline infused). The mean reduction ratio (RR) and associated significance levels (one-tailed t tests) are indicated and the fraction of the rats in each group which were in positive balance. This fraction is considerably greater than expected on a weight or bulk basis. This is illustrated in Fig. 3, showing that the rat eats less chow (in g) than diluted diet, despite the relative unpalatability of the latter.

A detailed study of the residual oral meal patterns was made for nine rats using 60–80 BL infusions such that a substantial OF1 persisted. In all of these rats the OF1 plus infusion was greater than 100 BL, and the body weight change was zero (equilibrium group). Under these conditions, the daytime OF1 was essentially abolished (Table 3), save for an occasional small meal (Fig. 4). Nocturnal feeding was reduced by a comparable amount (kcal), mainly through the lengthening of intermeal interval (less meals) and to a modest reduction in meal size (Table 3; Figs. 3 and 4).

Experiment 2

The addition of insulin to the infused glucose or saline led to the expected elevation of OF1 (and total intake) above the no-insulin condition. In the case of

<table>
<thead>
<tr>
<th>Solution</th>
<th>Mean RR</th>
<th>p</th>
<th>Fraction Gain- ing Body Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Oral + iv</td>
<td>Mean RR</td>
<td>p</td>
<td>Fraction Gain- ing Body Weight</td>
</tr>
<tr>
<td>2</td>
<td>85 ± 7</td>
<td>123.5 ± 3.5</td>
<td>0.72</td>
</tr>
<tr>
<td>5</td>
<td>87 ± 6</td>
<td>117.0 ± 3.6</td>
<td>0.02</td>
</tr>
<tr>
<td>6</td>
<td>80 ± 4</td>
<td>130.0 ± 4.7</td>
<td>0.62</td>
</tr>
<tr>
<td>Lipid</td>
<td>81 ± 6</td>
<td>163</td>
<td>0.23</td>
</tr>
<tr>
<td>Glucose</td>
<td>93</td>
<td>147</td>
<td>0.50</td>
</tr>
</tbody>
</table>

The mean residual OF1 of rats in this group was 30% body weight change was greatest on the 1st day of the infusion group, n = 13, showed stable body weight (mean 100 BL infusion, probably due to net shifts in fluid balance. This fraction is greater for fluid 2 than 5 (P < .05, U test on body weight changes).
FIG. 2. Long-term infusions (mainly liquid 6) for rat 90. Days 31-35 infusion was made hypertonic in NaCl without disruption of ongoing energy regulation (intakes presented as in Fig. 1).

FIG. 3. Cumulative meal pattern of rat 127 infused with liquid 5 and 2 kcal/h. For first 2 days (read upward), calorically diluted diet was available, and for next days regular chow was given. Oral intake (g) dropped at once with dietary switch.

FIG. 4. Cumulative meal patterns for rat 38, with days marked at right corresponding to Fig. 1. Note nocturnal residual feeding and increased intake soon after end of infusion (i.Inf.)

Table 3. Meal parameters of rats receiving continuous intravenous infusions

<table>
<thead>
<tr>
<th>Rat No.</th>
<th>Diet</th>
<th>No. of Meals per 12 h period</th>
<th>Meal Size Change (Sign)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BR  (sal)</td>
<td>BR (nut)</td>
</tr>
<tr>
<td>122</td>
<td>o</td>
<td>3  1 -2 4 3.5 -5</td>
<td>-</td>
</tr>
<tr>
<td>125</td>
<td>o</td>
<td>4  1 -3 8 2 -6</td>
<td>-</td>
</tr>
<tr>
<td>126</td>
<td>o</td>
<td>3  2 -1 5 6</td>
<td>-</td>
</tr>
<tr>
<td>123</td>
<td>o</td>
<td>4.5 9 -7.5 6.5 9 -3.5</td>
<td>-</td>
</tr>
<tr>
<td>124</td>
<td>o</td>
<td>0 0 -3 6 5 -1</td>
<td>-</td>
</tr>
<tr>
<td>127</td>
<td>d</td>
<td>2  9 -2 1 6 -1</td>
<td>-</td>
</tr>
<tr>
<td>128</td>
<td>d</td>
<td>4  1 -3 5 3 -2</td>
<td>-</td>
</tr>
<tr>
<td>197</td>
<td>d</td>
<td>4  0 -4 5 4.5 -5</td>
<td>-</td>
</tr>
<tr>
<td>193</td>
<td>d</td>
<td>3  1 -2 4.2 5 +5</td>
<td>-</td>
</tr>
<tr>
<td>Mean</td>
<td>all</td>
<td>3.6 0.8 -75% 5.2 3.8 -37%</td>
<td>-42% -26%</td>
</tr>
</tbody>
</table>

Average number of meals per day (2-16 days) in condition for rats receiving continuous intravenous infusion of liquid 5, 6 kcal/day. All rats served in saline control conditions: 161 meals/16 days for 6 rats on standard laboratory chow, o, and 6 meals/10 days for 3 rats with cellulose-diluted oral food, d, as well as the nutritive condition (267 meals/57 days per 6 rats, d; 106 meals/24 days for 3 rats, d). The meal size reduction (mean 0%) refers to diet o only. All of the data are dichotomized between bright (BR) and dark (DK) parts of the 24-h. P values are given by one-tailed sign tests.

Saline infusion, the normal 100 BL was elevated by some 48% using 10 U/day of insulin. The infusion of glucose plus insulin reduced this elevated control intake extremely efficiently (i.e., calorie for calorie). The results shown in Fig. 5 yield a mean RR of exactly unity except at the highest infusions. In the absence of exogenous insulin infusion, the RR was 0.52 (data from experiment 1) or 0.42 when additional long-term infusion data were added.

The insulin-plus-saline infusion produced a substantial body weight gain (mean +10.7 g/day). Despite the perfect caloric compensation when glucose and insulin were infused, the body weight gain was significantly lower in the latter condition (mean +3.8 g/day; t = 3.23, df = 67, P < .01).

Three rats additionally received parallel infusions of sorbitol and insulin. These infusions caused only a small reduction of OF1 from the saline control level of 31.4 to 26.2 g/day (RR = 0.28, infusion = 60 kcal/day). The body weight change was intermediate between that found with saline and glucose plus insulin.

The recorded meal patterns of a representative rat...
are shown in Fig. 6. During the saline-plus-insulin phase, oral meals were equally distributed throughout the 24 h, and meal size was particularly regular. During the glucose-plus-insulin phase, the number of meals was greatly reduced, but feeding was again equally distributed over 24 h. The sorbitol infusion had little effect on meal patterns.

**Experiment 3**

Results are considered for only those five rats showing stable body weight and tolerating the discontinuous infusion for 4–12 days. The RR was found to average 0.95 (compared to 100 BL in the discontinuous saline infusion condition). A regression analysis showed that the reduction of OFI was correlated with the amount infused \( r = 0.81, \text{df} = 41, P < .01 \), although the slope of the regression was only 0.72. This value is lower than the mean RR because of a nonlinear function, with relatively higher reductions in OFI for smaller infusions. All rats were in equilibrium during the nutritive infusion (mean body weight change = −0.6 g/day) but gained body weight (+3.3 g/day) during the saline control phase.

Both meal size and number were reduced by the discontinuous nutritive infusion. There was no apparent relation between the timing of spontaneous oral meals and the time since the last intravenous injection. Thus, cases of feeding soon after an injection were observed as frequently as following a long period without injection; further analysis of the data was therefore not performed.

**DISCUSSION**

The above results demonstrate that when metabolites are continuously infused directly into the systemic compartment there is a reduction in OFI. That reduction is, however, less than calculated from considerations of energy balance with the exceptions of exogenous insulin supplement (experiment 2) and discontinuous infusions (experiment 3).

Most of these findings are not adequately explained by theories which propose that adequate satiety (defined by the absence or reduction of feeding for the present purposes) is generated by the availability of metabolites at systemic receptors putatively involved in the control of food intake. Such theories have not received unanimous support, e.g., from studies employing acute intraperitoneal and intragastric loads of nutrients (2–4, 9, 12, 14, 17, 21, 23, 30, 31, 33).

A new conceptual framework appears necessary to incorporate these findings. Because energy regulation must be related to the dynamic processes of intermediary metabolism (5, 8, 14; M. I. Friedman and E. M. Stricker, personal communication), we believe it more appropriate to look for metering functions in power production—an instantaneous process—rather than its time integral, energy. We therefore propose an ischymetric (ischys = power; Gk.) theory, at the core of which are hypothetical receptor cells which monitor their own power production, or the turnover of metabolic substrates at their own intracellular level. These cells, actively involved in satiety, are ischymeters. These cells (which may be situated at one or a number of sites in the nervous system) are further presumed to be representative of the overall metabolism of the organism. This implies they may burn all available substrates as a function of both their effective concentration and that of the endogenous cofactors of their processing. A quantitative estimate of this multiple factor rate of

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**Fig. 6.** Cumulative meal pattern of rat 224 receiving a continuous infusion of insulin (10 U/24 h) with, for successive 2 day blocks, infusions of glucose (2.5 kcal/h), sorbitol (2.5 kcal/h), and saline (0.9%).
energy production is then supposed to be transduced into negative feedback signals acting on feeding control mechanisms. We shall now consider aspects of the current results which are compatible with this model of metering of nutrients.

Reduction Ratio (RR)

The RR was in the range 0.5-0.8 for a variety of solutions administered in the continuous intravenous mode. The RR was reasonably constant over a wide range of infusion rates (experiment 1). The fact that the total (intravenous + oral) intake was in excess of 100 BL, yet in many animals this excess was not accompanied by an excessive body weight gain (particularly notable since rats of this strain and age usually grow at 1-2g/day), suggests an incomplete metabolism of the infused substrates. The ischymetric model predicts that only the fraction of the infused metabolites that enters into power production will actually participate in satiety processes. The residual OFI is proportional to the energy deficit not covered by the infusions; it appears that the high residual OFI (total intake over 100 BL during infusions) is due to a poor utilization of the infusion with attendant energy leakage. This is not in the form of glycoseura or elevated rectal temperature. Thus, any improvement of the utilization of the infused nutrients, such as insulin coinfusion in experiment 2, will lead to a greater decrease in OFI.

In additional experiments (26) we have found that sorbitol, a sugar that is poorly metabolized by the rat (31), has similar effects on OFI as equicaloric glucose infusions. Sorbitol-infused rats do not, however, gain body weight; the effects of sorbitol are not likely to be due to nonspecific osmotic suppressions because they were not evident during reinfusion of insulin (Fig. 6) or when NaCl was added (Fig. 2). It remains possible that sorbitol infused in this way is better utilized than usually recognized.

Previous investigators (1, 2, 30) have reported failures to obtain suppressions of food intake with glucose infusions. This is probably because they infused only low amounts and the small OFI suppression was not significant (30) and/or the rats gained body weight (1). More recently, however, our earlier findings with glucose (26, 27) have been independently replicated (22) and held true across sex and strain (unpublished observations).

The lipid emulsions infused did not appear to be utilized to an appreciable extent, and the effects on OFI were minor, a noteworthy result in view of the poor tolerance of these fluids. A recent study employing injections of a palmite acid/albumin complex found similarly small effects on OFI at nontoxic doses (6). The toxic effects of the infusions of Intralipid have also been reported by Piquard et al. (22).

During glucidic infusions, the residual OFI was for calories rather than bulk, indicated by the cellulose-diluted diet result (experiment 1). A complementary argument in favor of a metabolic determinant of the residual OFI is found in the analysis of meal patterns. The intravenous infusion led to fewer meals, and the magnitude of the decrease in OFI was equal in both day and night phases. The residual oral meal size was correlated with the postmeal interval, and the average (meal size)/postmeal interval was 32 cal/min; this value is lower than reported values (15) found in our saline-infused control periods (35 cal/min by day and 49 cal/min by night). These numbers indicate the mean rate of utilization of orally ingested nutrients is reduced by about 22% during nutritive infusion.

Under normal feeding conditions, the observed meal pattern may be derived from the ischymetric model. Daytime lipolysis adds fatty acids to the metabolite pool, and so intermeal intervals are relatively long when compared with the nighttime when lipogenesis predominates (14). The continuous infusion of metabolites into the currently available pool should thus have identical effects at all parts of the 24-h cycle, and in particular intermeal intervals should be prolonged as utilization of the last meal is slowed. This was precisely the result obtained.

Metabolic Hormones and Orogastrointestinal Bypass

The RR of 0.5 observed for glucose infusions was increased to the theoretical maximum of 1.0 by the parallel infusion of insulin. The intravenous infusion will, of course, fail to stimulate the orogastric receptors which are known to give rise to reflex preparatory systemic events (18). In particular, the orally elicited first phase of insulin secretion (16, 16a, 32) will be eliminated, and only the direct systemic stimulation of insulin (and undoubtedly other metabolic hormones) will remain. The addition of exogenous insulin was designed to overcome such a putative deficiency of endogenous secretion, and the resultant increase in RR is consistent with the above reasoning. A similar result was obtained in rats bearing ventromedial hypothalamic lesions (28). In both cases, an abolition of the daily cyclicity in OFI was observed, which is expected with constant antilipolytic levels of insulin which will promote the rapid conversion of glucidic reserves into fat.

In experiment 3 the paradigm of the discontinuous infusion was introduced in order to improve the secretory responses to the metabolic stimulus. Such pulsed infusions will lead to a quasiwave-wave stimulus at the systemic level, and time-varying (high derivative) infusions of glucose are known to be more efficient stimuli for insulin secretion than are continuous (zero derivative) counterparts (7). Under conditions of oral feeding, the stimulation at both oral and gastric levels is high derivative, whereas the systemic absorption will give rise to a small positive derivative. Thus, two optimal events occur during oral feeding. First, oral stimulation prepares the system for incoming nutrients through the reflexly elicited supply of metabolic cofactors, and second a positive derivative in the postabsorp-
A Specific Appetite Interpretation?

The qualitative composition of the intravenous diet was found to influence OFI. The nutritionally less complete diets gave the largest residual OFI and lowest RR values. In some cases, notably glucose alone, the excessive oral intake was often associated with body weight gain. It is possible in these cases that the simplest form of ischymetric readjustment of energy intake is modulated by another process, namely specific appetite for the indispensable microelements not included in the infusion mixture. The oral diet that contains these elements is therefore ingested to excess at the compromise of energy homeostasis.

These phenomena were not observed in earlier studies (1) in which the same liquid diet was available orally as was infused intravenously giving RR = 1.0, although a similar continuous intragastric experiment gave RR = 0.5 0.7 (23). Under such conditions where the oral and intravenous diets are identical, the animals are unable to compensate for missing elements by overeating. There is recent evidence supporting our view of a specific appetite, in which dietary self-selection was modulated according to the nature of the intravenously infused diet (22).

The effects of amino acids remain unresolved. Casein hydrolysates injections (9) and infusions (1, 22) led to long-term suppressions of OFI, infusions of pure amino acids or of Trophye (essential amino acids with salts and vitamins) led to no suppression of food intake in our hands (26, unpublished experiments using Aminosol), whereas others have found an excessive suppression (22). We suggest that under ideal conditions amino acids have no suppressant effect on food intake (9). What is clear, however, is that coinfusion of glucose and amino acids leads to a larger effect on OFI than glucose alone can, however, is that coinfusion of glucose and amino acids leads to a larger effect on OFI than glucose alone can be. This is to be expected on the present specific appetite interpretation, when the mixture will furnish most necessary amino acids. Even with mixtures, however, some oral food intake appears necessary for the maintenance of body weight (24; unpublished observations).

In fact, even at the highest intravenous infusions the OFI rarely fell below 5 g/day. It is possible this residual intake does not reflect a specific appetite, but may represent a nonhomeostatic control over feeding, namely an "oral specific need" as we have analogously proposed for drinking (29). Such an intake would probably be adequate to maintain microorganism activity in the gastrointestinal (GI) tract; when oral intake is forcibly eliminated during parenteral alimentation, there is some GI atrophy (10). It is thus relevant that intravenous-only fed rats grow less rapidly than orally pair-fed controls (10), rabbits lose body weight (24), and growth is slowed in young rats infused as in the present experiment 1 (unpublished observations). The essential nature of a minimum oral intake is emphasized not only because of its implications for physiological regulations discussed above, but also for the additional psychological complications in human hyperalimentation (11).

In conclusion, a model for metering of energy balance was proposed which is founded in the multiple metabolic fuels and their impact at the level of the whole organism (5, 8, 25). This ischymetric metering involves the assessment of power production at the intracellular level; when this falls feeding is energized. This model was illustrated using the results from long-term infusion experiments. While it appears that the behavioral event of feeding is essentially controlled by ischymetric mechanisms, these are modulated by both specific appetite and "oral need" factors. Further long-term experiments will be required before firm statements may be made about the relative contributions of these factors (e.g., 22).

The demonstration that diets that are clearly nutritionally inadequate may activate specific appetites at the expense of energy balance (hence body weight maintenance) is of particular relevance to modern societies in which many purportedly complete semisynthetic foods are available and are often consumed to excess.

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