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Dietary Quinine Has a Nongustatory Effect on Food Intake in Rats[1]

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GUNION, M. W. AND R. H. PETERS. *Dietary quinine has a nongustatory effect on food intake in rats.* PHARMACOL BIOCHEM BEHAV 18(4) 593–599, 1983.—Recent data suggests that quinine adulteration of rats' maintenance diets may suppress food intake by postingestional (i.e., pharmacological or toxicological) mechanisms. This possibility was tested by increasing rats' rates of drug excretion prior to presentation of quinine maintenance diets. This treatment increased consumption of 3 concentrations (0.1, 0.2, 0.4%) of quinine diet in 2 separate experiments. In a third experiment, the same treatment did not alter consumption of quinine water in a 2 bottle test, suggesting that the increased consumption of quinine adulterated food was not due to a generalized decrease in the gustatory aversiveness of quinine. The data directly support the idea that quinine has postingestional effects which account for at least part of the suppression of food intake seen with quinine adulterated diets. The data further suggest that at least some of these effects occur postabsorptively.

Enzyme induction Drug metabolism Hepatic mixed-function microsomal oxidation system Phenobarbital
Dietary quinine Food intake Body weight

QUININE has long been used as a dietary adulterant in feeding (e.g. [14]). Addition of sufficient amounts of quinine to a maintenance diet results in decreased food intake and body weight in normal rats and in rats made obese by various experimental manipulations [12,17]. This effect of dietary quinine has commonly been presumed to be purely due to gustatory mechanisms. Quinine possesses a potent bitter taste, and will render food and fluids distasteful to rat [15,16] and human (uncontrolled personal observations) alike even in relatively small amounts.

Recently the notion that quinine affects food intake and body weight by its taste alone has been challenged. This challenge has come from data showing that quinine causes patterns of food intake changes different than those caused by other aversive dietary adulterants, which are themselves presumed to have few, if any, postingestive effects ([1, 9, 20] see also [16]). This difference between quinine and other adulterants has been interpreted as indirect evidence that quinine has toxic postingestional effects which influence food intake [9]. Two studies have suggested the possibility that taste aversions may be formed by quinine [1,19]. At best, however, these two studies can be considered only suggestive. Quinine was not actually used to condition an aversion in either report, and a conditioned aversion hypothesis is just one (albeit attractive) possible explanation for the results obtained. While these data certainly suggest that quinine may have postingestive effects on food intake, direct evidence showing a postingestional effect of quinine on the food intake of normal rats is lacking.

Data from our and other laboratories show that the effects of quinine on food intake follow a characteristic pattern [1, 9, 16]. Rats placed on a quinine diet immediately decrease their daily food intake, then gradually increase it over the next several days, often to normal or near-normal levels. In examining this pattern of changes in food intake, we noted that the recovery of intake on these quinine adulterated diets roughly followed the time course typical of induction of the mixed-function hepatic microsomal oxidation system [2]. This is the enzyme system of the liver responsible for the excretion of quinine, many other drugs, and steroid hormones. This enzyme system, when faced with a sufficient load for a sufficient duration, will increase its oxidating capacity through an increase in the rate of synthesis of its consituents. Since quinine is known to be oxidized by this system [19], it is probably capable of inducing it as well [2]. Thus, a progressive increase in the rate of quinine excretion over the first few days of feeding on a quinine diet could be expected. The progressive increase in food intake seen at the same time, then, could be due to an increasing ability of the animal to excrete the drug, at least in part. Such a hypothesis clearly indicates that dietary quinine must have effects on food intake that are postingestional, even postabsorptive, in nature.

If the increase in intake of quinine diets over days is due to hepatic enzyme induction and a subsequent increase in the rate of quinine excretion, then induction of this enzyme system prior to beginning maintenance on a quinine diet should result in greater quinine intake in enzyme-induced than in non-induced animals. Such an outcome would clearly indicate postingestional effects of quinine on food intake. We decided to test this hypothesis by injecting rats with phenobarbital for several days prior to initiation of maintenance on a quinine adulterated diet. Phenobarbital is com-

[1]Requests for reprints should be addressed to R. H. P. A preliminary report of this work was presented at the annual meeting of the Western Psychological Association, Honolulu, 1980. M. W. G. is now at the Department of Psychology, U.C.L.A., Los Angeles, CA 90024.

monly used to induce this enzyme system [2], and it has specifically been shown that treatment with phenobarbital increases the rate of quinine metabolism by rat liver both in vivo and in vitro [19].

EXPERIMENT 1

Part A

METHOD

Subjects

Subjects were female Long-Evans hooded rats (Blue Spruce Farms, Altamont, NY) weighing 248–290 g at the beginning of the experiment. They were housed individually in standard hanging cages under a 12/12 hour light/dark cycle in a separate room (24°C). Tap water was continuously available. They were fed as described below.

Diets

Rats were initially maintained on standard laboratory pellets (Teklad Mouse and Rat (4% fat), Winfield, IA). Later they were maintained on powdered laboratory chow (Purina diet No. 5001, St. Louis, MO). The powdered chow was delivered in glass ointment jars (87 mm high by 70 mm wide) placed in the cage and held to the cage front by a wire loop. Adulterated food was prepared by adding 0.1% or 0.2% (w/w) quinine sulfate (Sigma Chemical Company, St. Louis) to the powdered chow.

Procedure and Groups

Rats were fed powdered chow for 7 days before the experiment began. The experiment was divided into three periods: a baseline determination period (days 1–6), a drug injection period (days 7–13), and a test diet period (days 14–28). Body weights (nearest gram) and food intake (nearest 0.1 gram, spillage corrected) were determined daily at the midpoint of the light phase beginning with the baseline period. Spillage was collected on paper towels placed beneath the cage.

Drug injections were administered twice daily during the injection period. Injections were given immediately after light onset and immediately before light offset. The first injection was given at the end of the light phase on day 5, 6 hr after food intake and body weight were measured on that day. The last injection was given at the beginning of the light period of day 13. The dose and injection schedule imitated the dose and administration used by Saggers *et al.* [19], who found the in vivo rate of quinine metabolism increased by approximately 4 times. Our schedule and dose increased the activity of this enzyme system by approximately 5 times in an in vitro test [5]. The phenobarbital solution was prepared by first adding phenobarbituric acid (30 mg/kg; Gaines Chemical Company, Pennsville, NJ) to distilled water; then a just sufficient amount of sodium hydroxide (pellets) was added to bring the drug into solution. Drug prepared in this manner caused no obvious discomfort to the animals when injected. All injections were given intraperitoneally in a volume of 1.0 ml/kg.

A total of 6 gooups were used in this experiment. During the injection period 3 groups received phenobarbital and 3 groups received saline (0.9% w/v). For the diet period the drug treatment was crossed with diet concentration. One group from each drug treatment continued maintenance on plain (0.0% quinine) powdered chow; one group from each drug treatment began maintenance on 0.1% quinine chow; and the remaining group from each drug treatment began maintenance on 0.2% quinine chow. The quinine diets were introduced in the middle of the light period on day 13, 6 hr after the last injection.

The phenobarbital-plain diet group contained 7 rats; the other 5 groups had 8 animals each.

Statistical Analysis

Baseline period and injection period food intakes and body weights were analyzed by analysis of variance (ANOVA). Intakes and weights for the first 10 days of the diet period were analyzed cell against cell using Dunn's multiple comparison procedure (all tests were specified a priori [8]). Comparisons across the entire diet period were also made using Dunn's procedure. Error terms for Dunn's procedure were derived from weighted means analysis of covariance for the diet period. The covariate used was the average baseline measure of the dependent variable under consideration.

RESULTS

Prior treatment with phenobarbital produced elevated intakes of quinine adulterated food for the first several days of exposure to these diets (Fig. 1). Phenobarbital treated rats ate 41% more 0.1% quinine diet for the first 2 days, and 46% more 0.2% quinine diet for the first 3 days, than did saline treated animals fed the same diet ($p<0.01$ for all 5 comparisons).

Surprisingly, the intake of the saline treated animals caught, then surpassed the intake of phenobarbital rats a few days after introduction of the quinine diets and cessation of the drug treatment. This difference was significant for the 0.1% diet on day 17 ($p<0.05$) and for the 0.2% diet on day 19 ($p<0.01$). Inspection of the data shows that this was not due to decreases in intakes by the phenobarbital rats, but instead was due to a marked delay by these rats in increasing their intakes over time as the saline treated rats did.

Quinine adulteration substantially decreased food intakes of saline treated rats. Over the entire 15 day quinine diet period, saline rats fed the 0.1% quinine diet ate 33% less than saline rats fed the unadulterated diet, and saline rats fed the 0.2% quinine diet ate 45% less than saline rats fed the unadulterated diet (both $p<0.01$). Additionally, saline rats fed the 0.2% diet ate less than saline rats fed the 0.1% diet ($p<0.01$).

Withdrawal of the phenobarbital treatment was sufficient to cause a significant, though transient, suppression of food intake. Phenobarbital rats fed the unadulterated diet ate less than saline rats fed the unadulterated diet on days 15 ($p<0.01$), 16 ($p<0.01$), and 17 ($p<0.05$). The one day delay between cessation of drug injection (day 13) and suppressed food intake is probably due to the relatively long half-life of phenobarbital [6]. During the injection period there was a significant effect of phenobarbital treatment on food intake. Phenobarbital treated rats ate 15% more food than did saline injected rats over the seven day injection period, $F(1,41)=24.37$, $p<0.0001$. There were no differences among the groups during the baseline period.

The body weight data are presented in Table 1. Phenobarbital injection caused a significant 9.6 g increase in body weight compared to saline during the injection period, $F(1,41)=8.68$, $p<0.006$, for the entire injection period. In

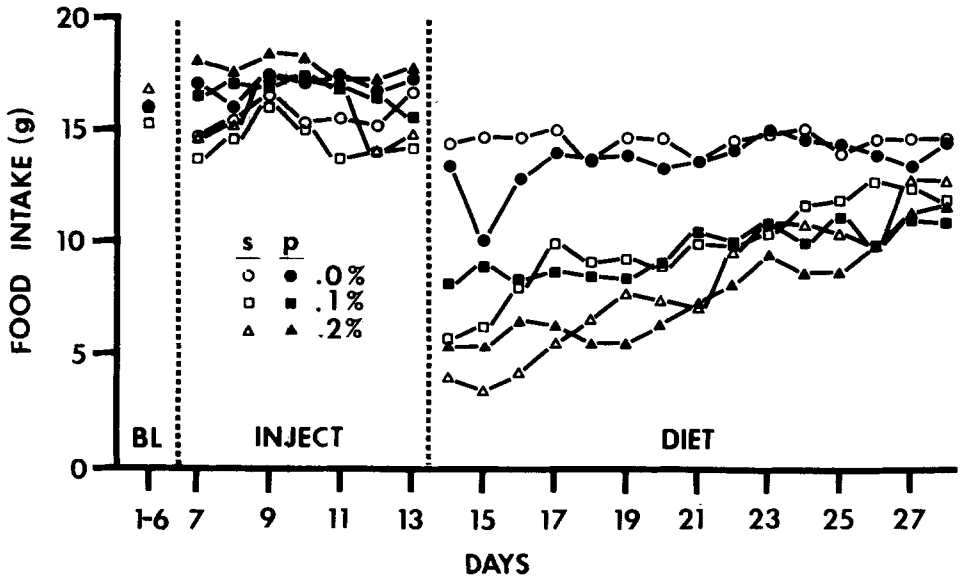

FIG. 1. Experiment 1A. Group mean food intakes. Abbreviations: S—saline, P—phenobarbital, BL—baseline period, INJECT—injection period, DIET—diet period. Percentage numbers indicate the concentration of quinine in the diet.

general, the phenobarbital treatment conferred a long-lasting increase in body weight on the quinine diet animals, an increase which outlasted the increased quinine diet consumption of these animals. The phenobarbital rats given quinine diets weighed significantly more than same-diet saline rats for the first 9 days after introduction of the quinine diets ($p<0.01$ for both comparisons on all 9 days except 0.2% diet on days 20 and 22; those days, $p<0.05$; on day 23 only the 0.1% groups were significantly different, $p<0.01$). It is interesting to note that this prolonged increase in body weight was not seen in phenobarbital rats which remained on plain chow. Although these rats weighed 14 g more than their saline controls on the last injection day (day 13), they had almost completely lost this excess weight by the next day (mean difference of 3 g on day 14). From that point they did not differ in body weight from saline treated animals.

Part B

Part B was a separate experiment highly similar to but run at a different time than Part A. It was conducted to examine the effect of the phenobarbital treatment on the consumption of a more aversive quinine diet than those used in Part A.

METHOD

Subjects, diets, and housing were as in Part A, with two

TABLE 1

EXPERIMENT 1A. GROUP MEAN BODY WEIGHTS (g) AT VARIOUS POINTS DURING THE EXPERIMENT

		Baseline Period	Injection Period	Diet Period				
	Day:	Mean	13	14	17	20	24	28
% Quinine	Drug							
0.0%	S	274	278	280	282	283	283	287
	P	277	291	283	283	284	286	288
0.1%	S	272	277	268	263	259	261	262
	P	277	289	279	272	269	268	266
0.2%	S	271	278	265	254	250	251	255
	P	272	289	274	263	255	252	255

Day 13 was the last day of the injection period; days 14–28 constituted the diet period. Abbreviations: S—saline, P—phenobarbital.

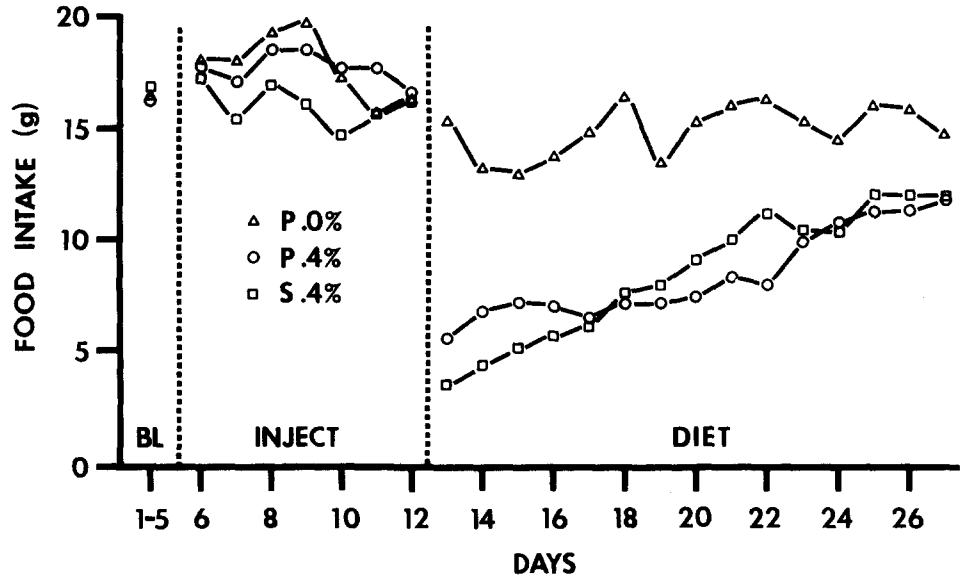

FIG. 2. Experiment 1B. Group mean food intakes. Abbreviations: S—saline, P—phenobarbital, BL—baseline period, INJECT—injection period, DIET—diet period. Percentage numbers indicate the concentration of quinine in the diet.

exceptions: the rats weighed 206–251 g at the beginning of the experiment, and a 0.4% (w/w) quinine sulfate diet was used.

Procedure and Groups

The procedure of Part B was identical with that of Part A with the exceptions noted here. During the 5 day baseline period all rats received 2 daily injections of 0.9% saline at the same times as drug administration would later occur during the injection period. Only 3 groups were used in this experiment. One group received saline during the drug injection period, and was given the quinine diet (n=7). The second group received phenobarbital during the drug injection period, and was given plain chow during the diet period (n=8). The final group received phenobarbital during the drug injection period, and was given the quinine diet during the diet period (n=8).

The data were analyzed with one-tailed *t*-tests specified a priori.

RESULTS

As in Part A, prior treatment with phenobarbital increased the consumption of quinine adulterated food for the first few days of exposure to the diet. As shown in Fig. 2, phenobarbital rats ate 56% more than saline treated rats for the first 4 days of access to the 0.4% quinine diet. This effect was significant for the first 3 days (day 13: $t(13)=2.740$, $p<0.01$; day 14: $t(13)=2.362$, $p<0.025$; day 15, $t(13)=1.867$; $p<0.05$).

In Part A, saline groups given the quinine diets increased their intakes to above those of phenobarbital rats after the first few days of the diet period. This phenomenon was also observed in Part B. The mean intake of saline rats was more than that of phenobarbital rats on days 18–23, although this mean difference reached marginal statistical reliability only on day 22, $t(13)=1.726$, $p<0.06$.

As found in Part A, phenobarbital caused an increase (7%) in food intake during the injection period compared to baseline levels, $t(15)=2.812$, $p<0.01$; combined phenobarbital groups. Withdrawal of phenobarbital treatment caused an 11% decrease in the food intake of the rats fed the plain diet (entire diet period compared to entire baseline period; $t(7)=3.204$; $p<0.01$). The quinine adulteration of the diet also produced a clear decrease in food intake. Saline treated rats fed the quinine diet ate a mean of 46% less over the entire diet period than over the entire injection period, $t(6)=12.824$, $p<0.001$.

The body weight data (Table 2) appear virtually identical to those from Part A. Phenobarbital produced a significant increase in body weight during the quinine injection period-compared to baseline, $t(14)=11.636$, $p<0.001$, combined phenobarbital groups; adjusted for saline group weight gains. As in Part A, this elevated body weight appeared to be retained by the phenobarbital animals given the quinine diet; these rats showed a mean body weight greater than that of saline rats throughout the dark period. However, this difference never reached statistical significance on any of the first 10 days of the diet period (all $ts(13)<1.366$, $p>0.05$). Maintenance on the quinine diet did cause a significant loss of body weight. Saline rats fed the quinine diet weighed 7% less over the entire diet period than during the injection period, $t(6)=7.359$, $p<0.005$.

DISCUSSION

Rats with increased rates of drug metabolism (i.e., quinine clearance) ate more of 3 quinine adulterated foods in 2 separate experiments. These data, then, seem to suggest that some postingestional effect is involved in the suppression of food intake by this alkaloid. However, alternative

TABLE 2

EXPERIMENT 1B. GROUP MEAN BODY WEIGHTS (g) AT VARIOUS POINTS DURING THE EXPERIMENT

		Baseline Period	Injection Period	Diet Period				
	Day:	Mean	12	13	16	19	23	27
% Quinine	Drug							
0.0%	P	228	247	244	246	250	255	257
0.4%	S	234	245	229	219	213	217	222
0.4%	P	232	251	236	229	220	221	225

Day 12 was the last day of the injection period; days 13–27 constituted the diet period. Abbreviations: S—saline, P—phenobarbital.

explanations exist. Phenobarbital is well known as a powerful psychotrophic agent [6]. It is possible that this effect of phenobarbital, rather than its effect on drug metabolism, may have caused the increased ingestion of quinine food. Rats treated with this drug may find quinine less distasteful, less unpalatable, than do saline treated rats. It is also possible that phenobarbital treatment may have attenuated any neophobia associated with the introduction of a quinine adulterated diet, thus allowing increased food intake [13].

Experiment 2 was conducted to test these possibilities.

EXPERIMENT 2

If phenobarbital increases consumption of quinine food by making the taste of quinine less aversive or by reducing neophobia, then an increased acceptance of quinine should be found in other situations as well. A 2 bottle preference test comparing the relative consumption of quinine water and tap water was used to test for a generalized increase in quinine acceptance.

METHOD

Subjects and housing were identical to Experiment 1, except that the rats were 110–120 days old at the beginning of the experiment.

Procedure

Eight rats were injected with phenobarbital and 8 with saline as in the previous experiments. Beginning on the 7th hour after the last injection, and continuing for the 4 succeeding 12 hour periods (6 hr light plus 6 hr dark), the single water bottle was replaced with two water bottles. One bottle contained 1 of 4 solutions of quinine adulterated tap water, and the other contained plain tap water. The bottles were positioned on the cage front on either side of the position occupied previously by the single water bottle. Side of the cage was determined randomly. At the end of each of the 4 12 hr periods the bottles were removed and replaced with two others, another quinine solution and another bottle of plain tap water. Order of presentation was counterbalanced for time since the last injection, concentration, and presentation during the light or dark. The concentrations of quinine water used (−4.75, −4.00, −3.25, and −2.50 log%) were taken from previous work [15], where they produced percentage intakes as quinine fluid ranging from 50% (−4.75 log%) to 12% (−2.50 log%). Food was available ad lib on the cage floor throughout the experiment.

TABLE 3

EXPERIMENT 2. EFFECTS OF PHENOBARBITAL TREATMENT ON CONSUMPTION OF QUININE WATER

	Quinine concentration		
Group	−4.75 log %	−4.00 log %	−2.50 log %
Phenobarbital	54 ± 11	53 ± 11	18 ± 10
Saline	39 ± 7	58 ± 13	15 ± 9

Data are expressed as mean percentage (±standard error) of total 12 hr fluid intake taken as quinine water.

Statistical Analysis

Data were derived as the percentage of total fluid intake taken as quinine water during the 12 hr period. ANOVA was used to analyze the data.

RESULTS AND DISCUSSION

After the experiment a leak in one −3.25 log% bottle was discovered. Since it was not possible to clearly determine which data points were contaminated, all data from the −3.25 quinine concentration were excluded from the analysis.

Rats given phenobarbital were neither less nor more sensitive to quinine water than were saline treated controls (Table 3). While a significant effect of quinine concentration on quinine fluid intake was observed, $F(2,28)=8.79$, $p<0.001$, no significant effects of drug treatment, $F(1,14)=0.22$, $p>0.64$, or drug treatment × quinine concentration interaction, $F(2,28)=0.51$, $p>0.60$, were seen.

GENERAL DISCUSSION

Induction of the enzyme system responsible for quinine

degradation increased the consumption of quinine adulterated foods. This effect on food intake could not be ascribed to a decrease in the gustatory aversiveness of quinine or to a decrease in neophobia. These data therefore seem to indicate that quinine has effects on food intake which are postingestional in nature. The data further indicate that at least some of these effects occur postabsorptively; therefore, simple gastrointestinal irritation [18] does not account for the entirety of quinine's postingestional effect on food intake.

One alternative explanation for the results obtained here is that phenobarbital administration may have disrupted the establishment of a learned taste aversion which normally accounts for part of the decreased consumption of quinine adulterated diets. Although we cannot rule out this possibility, we think it a less likely explanation. First, it does not account for the consistent finding that saline treated rats ate more quinine food than did phenobarbital treated rats during a discrete period beginning several days after introduction of the quinine diets. Under a "disruption of learned taste aversion" hypothesis one of two outcomes would be expected: (a) the food intake of phenobarbital rats would have shown a sharp drop several days after cessation of phenobarbital administration as drug inhibition of the learned aversion abated and the aversion subsequently formed; or (b) the food intakes of phenobarbital rats would have remained permanently above those of saline treated rats, since the learning of the aversion would have been permanently blocked by prior experience with an unconditioned stimulus (i.e., phenobarbital; [3]). Neither outcome (a) or (b) was found. Second, postulating the disruption of a learned taste aversion by phenobarbital adds unnecessary complexity. Such an explanation requires that (a) the quinine adulterated foods used here be capable of forming a learned taste aversion in the protocol employed, (b) that such an aversion be disrupted by prior phenobarbital administration as used here, and (c) that some component of the quinine diet hypophagia seen here in saline treated animals be attributable to this learned taste aversion. Extant data only suggest that (b), and perhaps (a), could occur; (c) is entirely unproven. Our hypothesis that phenobarbital temporarily enhanced quinine excretion and thus led to increased food intake is a much simpler one, and well within known physiology and pharmacology. We note that even if the disruption of a learned taste aversion is involved in the effects found here, this still suggests that the basic conclusion of this report is correct—that is, that quinine has postingestive effects which alter food intake.

We are not proposing that postingestional effects of quinine are solely responsible for the decreased food consumption produced by its use. Indeed, the magnitude of the postingestional contribution to quinine diet hypophagia is unclear. Upon initial inspection it appears that phenobarbital ameliorates the effect of dietary quinine relatively slightly; after all, the treatment blocked only 20–30% of the decrease in intake due to quinine. This same effect, however, also constitutes a 41–56% increase in food intake compared to same-diet saline treated rats. Further, it must be noted that withdrawal of phenobarbital treatment caused a strong suppression of food intake in plain chow animals relative to their saline controls. This suppression of food intake occurred at the same time that phenobarbital rats fed quinine diets were eating significantly more than their saline controls. Thus the effect of enzyme induction on quinine diet consumption was very probably diminished by the withdrawal of phenobarbital, and might otherwise have appeared substantially larger. So, while the exact magnitude of the enzyme induction effect on food intake is uncertain, it can be viewed as being quite substantial, and probably was actually much larger than was shown by these experiments.

The data presented here suggest that enzyme induction probably plays little if any role in the recovery of food intake after the introduction of quinine. This suggestion is based on the observation that the food intakes of saline treated rats given quinine diets not only reached, but actually surpassed, the intakes of phenobarbital rats after a few days exposure to the quinine diets. If the effect of phenobarbital had been merely to give a "head start" in increasing quinine metabolism rates, then saline rats should never have surpassed the intakes of phenobarbital rats, but only equalled them. The data appear more consistent with the possibility that enzyme induction delayed some necessary postingestional adaptation to quinine. This adaptation to a postingestional effect of quinine might have been delayed in the phenobarbital treated rats because of the increased rate of quinine excretion these rats initially enjoyed. This conjecture is illustrated by all 3 quinine concentrations, but is seen most clearly in Experiment 1-B (0.4% quinine diet). At first the induced enzyme system clears quinine from the animal relatively rapidly and food intakes are elevated above control (days 13–14); then the induction effect fades and food intakes fall toward and then below control (days 15–17); and finally the rat adapts on its own, and food intakes of phenobarbital treated rats merge with those of saline controls (18–21).

We do not mean the preceding discussion to imply that only a yet-unknown postingestional adaptation to dietary quinine is involved in the recovery of food intake seen in the saline treated rats. Other nongustatory processes are probably also involved, especially the defense of body weight (e.g. [10]). Exactly what relationship exists between a postingestional adaptation to dietary quinine and the defense of body weight (and other factors) is certainly unclear at present.

Labelling the reduction of food intake due to dietary quinine as a "toxic" effect of this material has been purposely avoided here. While it is certainly clear that quinine can have toxic effects by either peripheral or central actions [16], it is not clear that "toxicity" is necessarily always responsible for the postingestional component of the reduction in food intake. Since quinine is known to have direct central effects, it is not unreasonable to think that quinine might have direct effects on central feeding or feeding-related systems. For example, quinine could alter the hedonics (taste or reward) of food intake in a manner analogous to other substances [4, 11, 22]. Further, it has been demonstrated that quinine can affect both the release of insulin from, and the oxidation of glucose by, isolated pancreatic islets [7]. An effect of this type might certainly affect food intake, but not necessarily be "toxic" in nature. We note that even if the label "toxic" eventually proves applicable, quinine may still serve as a useful probe in food intake and weight regulation research if the responsible effects are identified and shown to be relevant.

In the last several decades many feeding studies have been done predicated on the assumption that quinine reduces food intake by a purely gustatory mechanism. Given the accumulating evidence that there is more to quinine's effects on feeding than meets the taste bud, interpretation of these studies now must be made with extreme caution. Finding a method that would allow differentiation between the gustatory effects and the postingestional effects on food intake

would make reinterpretation of these studies much easier, and might actually extract new information from them. The enzyme induction approach used in the work presented here may be such a method. For example, the relative contributions of preabsorptive and postabsorptive components in ventromedial hypothalamic (VMH) hypophagia to quinine diets might be ascertained by pretreating VMH rats to increase their rates of quinine excretion [5], and then determining the effect of this pretreatment on their food intakes. Examination of other obesity syndromes in a similar manner might show theoretically important and experimentally useful similarities and differences among them.

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