

Dietary effects on tyrosine availability and catecholamine synthesis in the central nervous system: possible relevance to the control of protein intake

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Contemporary neuroscience holds that central nervous system (CNS) function ultimately derives from the organization of neurons into complex associations analogous to electrical circuits. For these circuits to function, however, the neurons must be able to communicate with one another; in fact, they must exchange small electrical impulses. While some neurons accomplish this task by direct cellular contact, the primary mechanism appears to involve neurotransmitters. Neurotransmitters are molecules, released by neurons when they are electrically active, that modify electrical activity on adjacent neurons. Thus, neurotransmitters are key molecules in interneuronal communications, and in the functioning of the brain (Cooper *et al.* 1991).

Because of the central role of neurotransmitters, it is not surprising to find that factors which influence their synthesis and release modify CNS function. Indeed, many therapeutically-useful agents exert their biological effects by influencing the synthesis and/or release of neurotransmitters. Diet also appears to influence the synthesis and release of certain neurotransmitters. Some findings suggest that brain function is modified as a result. In the present article, we discuss the manner in which diet influences transmitter synthesis and release, and possibly function, using a particular example, dopamine (DA). DA is a low-molecular-weight neurotransmitter derived from the non-essential amino acid tyrosine. Its rate of synthesis in neurons is directly influenced by the local supply of tyrosine. Because the ingestion of food modifies the availability of tyrosine to the CNS, diet is thereby able to influence CNS DA synthesis; this diet–neurotransmitter relationship might participate in brain circuits that regulate appetite.

DOPAMINE SYNTHESIS: RELATIONSHIP TO TYROSINE SUPPLY

DA is synthesized in neurons from L-tyrosine in a two-step reaction. First, the amino acid is converted to dihydroxyphenylalanine (DOPA) in a reaction mediated by tyrosine hydroxylase (*EC* 1.14.16.2). DOPA is subsequently decarboxylated to DA by aromatic L-amino acid decarboxylase (*EC* 4.1.1.28). DA is the endproduct in neurons that utilize it as a neurotransmitter (Fig. 1). In other neurons, DA may be further converted to noradrenaline or adrenaline, if the appropriate enzymes are present. Each of these three compounds, known collectively as catecholamines, function as neurotransmitters (Cooper *et al.* 1991).

The initial step in this pathway, tyrosine hydroxylation, is rate-limiting and, thus, controls the synthesis rate through the entire pathway (Cooper *et al.* 1991). Tyrosine hydroxylase, which catalyses the reaction, has multiple controls on its activity. One of these is the local availability of substrate; increases or decreases in tyrosine level directly modify the rate of hydroxylation. However, this relationship holds only in DA neurons

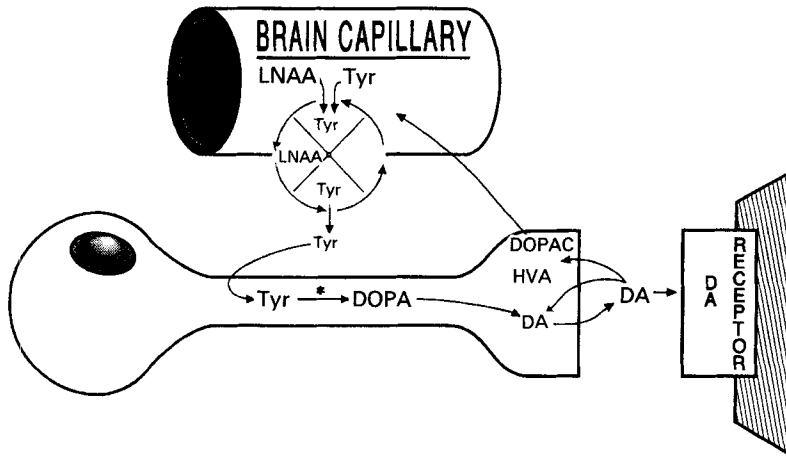


Fig. 1. Tyrosine (Tyr) availability and dopamine (DA) synthesis in neurons. Tyr is converted to DA by a two-step reaction, mediated by tyrosine 3-hydroxylase (*EC* 1.14.16.2; Tyr→dihydroxyphenylalanine (DOPA)) and aromatic L-amino acid decarboxylase (*EC* 4.1.1.28; DOPA→DA). Monoamine oxidase (*EC* 1.4.3.4) initiates the catabolism of DA to homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC), the principal DA metabolites in the CNS. *Rate-limiting step in DA formation, Tyr hydroxylation. The drug NSD-1015 blocks the decarboxylation of DOPA to DA. Tyr competes with other large neutral amino acids (LNAA) for uptake into brain (and retina).

that are actively firing, as is amply illustrated by studies in retina. The retina (a portion of the CNS) contains a subpopulation of interneurons that utilize DA as a neurotransmitter. *In vivo*, these neurons are quiescent in the dark, but fire actively in the light. They show this light activation biochemically, as well as electrically; tyrosine hydroxylase activity is low during the dark period, and increases substantially soon after the lights are turned on (Iuvone *et al.* 1978*a,b*; Fernstrom *et al.* 1986*b*). This 'physiological' means of activation (light) is what makes the retinal DA neurons so interesting to use as a model to examine biochemical effects of neuronal activation; in brain, the most accessible groups of DA neurons are fairly inactive, and require pharmacological treatments to stimulate them (Scally *et al.* 1977).

When light activation occurs in retinal DA neurons, tyrosine hydroxylation becomes very responsive to changes in local tyrosine concentration. Indeed, an injection of tyrosine into rats during the light period, which causes a 2–3-fold rise in retinal tyrosine levels, produces a highly significant increase in retinal tyrosine hydroxylation rate (Fernstrom *et al.* 1986*b*), which is an excellent index of DA synthesis rate (Carlsson & Lindqvist, 1978). This effect on hydroxylation rate is absent when the study is performed in the dark (Table 1). A similar effect can be obtained in a group of brain DA neurons, nigrostriatal DA neurons, whose firing rate has been increased by a drug (haloperidol, a DA receptor antagonist) (Scally *et al.* 1977). In the one set of brain DA neurons known to have an unusually high rate of firing, i.e. some mesocortical DA neurons, tyrosine administration has also been reported to stimulate hydroxylation rate (Bradberry *et al.* 1989).

Table 1. *Effect of tyrosine injection on the rate of tyrosine hydroxylation (dihydroxyphenylalanine (DOPA) synthesis) in retinas from normal rats exposed to light or dark (From Fernstrom et al. 1986b)*

(Mean values with their standard errors. Groups of six rats received tyrosine methylester (250 mg/kg intraperitoneally (ip)) or vehicle. After 90 min, all rats received NSD-1015 (100 mg/kg ip; a drug that blocks the decarboxylation of DOPA) and were killed 30 min later. For light-exposed rats, the experiment began 3 h after the onset of the daily light period. For rats studied in the dark, the experiment also began 3 h after the daily dark period ended, but the lights remained off during this interval and the experimental period)

Treatment	Tyrosine				Retinal DOPA synthesis (pmol/mg protein)	
	Serum (nmol/ml)		Retinal (nmol/mg protein)		Mean	SE
	Mean	SE	Mean	SE		
Light: Vehicle	76	2	2.8	0.2	8.2	0.5
Tyrosine	167	11*	7.4	0.7*	13.2	0.5*
Dark: Vehicle	120	8	3.0	0.2	4.1	0.5
Tyrosine	339	11*	6.2	0.8*	4.1	0.5

Mean values were significantly different from those of rats given vehicle under the same lighting conditions: * $P < 0.05$.

COMPETITIVE TRANSPORT OF TYROSINE INTO BRAIN AND RETINA

Since a large increment in retinal tyrosine level, induced pharmacologically by an injection of the amino acid, stimulates hydroxylation rate in DA neurons activated physiologically by light, it was of interest to ascertain whether hydroxylation rate would also increase in these neurons in response to a physiologically-induced increase in retinal tyrosine. We suspected that the physiological treatment most likely to produce such an effect was the ingestion of a high-protein meal, since it was known to induce a 2-fold or greater rise in brain tyrosine levels (Fernstrom & Faller, 1978). However, how could such an effect observed in brain be anticipated in retina?

The changes in brain tyrosine concentration that accompany a meal are known to follow indirectly from the effects of the meal on the transport of tyrosine into brain. Tyrosine uptake into brain occurs via a transport carrier, located at the blood-brain barrier, that is shared with several other large neutral amino acids (LNAA; primarily phenylalanine, tryptophan, leucine, isoleucine and valine). The transporter is competitive; thus, brain tyrosine uptake and levels are influenced not simply by tyrosine concentrations in blood, but also by the concentrations of the other LNAA (Fig. 1; Pardridge & Oldendorf, 1977). After rats ingest a 400 g protein/kg diet meal, brain tyrosine concentrations rise because blood tyrosine levels rise much more proportionally than the blood concentrations of its LNAA competitors (Fernstrom & Faller, 1978).

The retina is also found to have a 'barrier' to the blood, termed the 'blood-retina barrier'. It shares many properties in common with the blood-brain barrier but, at the time of these studies, it was not clear if a competitive LNAA transporter existed at the blood-retina barrier as it does at the blood-brain barrier. One could not predict with confidence, therefore, whether the effects of meals on retinal tyrosine levels would be like those on brain tyrosine levels. Hence, before exploring for diet effects on retinal

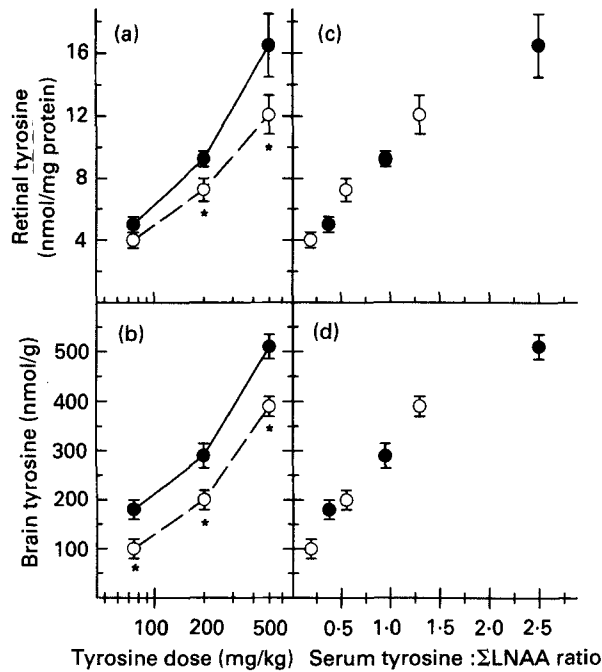


Fig. 2. Dose effects of tyrosine injection, alone or with other large neutral amino acids (LNAA), on retinal and brain tyrosine levels. Groups of rats received tyrosine intraperitoneally (at the indicated doses of free tyrosine) and 5 min later water (●) or LNAA (○; combined dose 270 mg/kg). They were then killed 55 min later. Values are means with their standard errors represented by vertical bars. (a, b), Brain or retinal tyrosine level *v.* tyrosine dose; (c, d), tyrosine level *v.* the serum tyrosine:total (Σ)LNAA ratio. The effects of tyrosine dose and LNAA on retinal and brain tyrosine levels were significant ($P < 0.01$; ANOVA). Mean values were significantly different from those for the group receiving tyrosine alone at the same dose: $**P < 0.01$ (*t* test). (Redrawn from Fernstrom *et al.* 1986a).

tyrosine levels, we performed studies to test for the presence (or absence) of competitive LNAA transport into retina. For these studies, we employed an approach used previously to demonstrate competitive transport into brain (Chirigos *et al.* 1960); we studied the ability of LNAA, when co-administered with tyrosine, to antagonize a tyrosine-induced rise in retinal tyrosine levels. In the key experiment, rats received an injection of tyrosine (one of three doses) alone or in combination with several other LNAA (Fig. 2). A short time later, the animals were killed, and retinal and brain (the positive control) tyrosine concentrations were measured. In both treatment groups, retinal and brain tyrosine levels rose with increasing tyrosine dose. However, in rats receiving other LNAA along with tyrosine, these increments were smaller (Fig. 2a and b). This antagonism was specific; it could not be elicited by co-administering acidic amino acids instead of LNAA (acidic amino acids are transported into brain by a carrier not shared with the LNAA (Oldendorf, 1971; Pardridge & Oldendorf, 1977)). The findings from this study were also plotted as retinal or brain tyrosine *v.* the 'serum tyrosine:total (Σ)LNAA ratio' (Fig. 2c and d). This ratio is simply the serum tyrosine level divided by the sum of the serum concentrations of its LNAA competitors (primarily tryptophan, phenylalanine, leucine, isoleucine, valine). In previous studies, it had been shown to

reflect accurately the competitive uptake of this amino acid into brain (Fernstrom, 1990). The serum tyrosine: Σ LNAA ratio appeared to do so in this study as well, for both brain and retina, since the data appear to fall on a single line for each plot (indicating that the ratio accurately predicts neuronal tyrosine levels under both treatment conditions). These results underscore the conclusion that there is competitive LNAA transport of tyrosine into retina, a position which has recently been substantiated using other methods (Tornquist & Alm, 1986).

EFFECT OF FOOD ON CNS TYROSINE LEVELS AND DA SYNTHESIS

Based on the previously described results, we concluded that retinal tyrosine levels should behave like brain tyrosine levels when rats consume single meals, since the effects of the meal on brain tyrosine may be interpreted on the basis of post-meal changes in the serum LNAA pattern (in particular, the serum tyrosine: Σ LNAA ratio) and, thus, competitive transport. We then proceeded to examine whether the ingestion of a high protein meal by rats would increase retinal tyrosine levels by a magnitude similar to that seen previously in brain, and if so, whether tyrosine hydroxylation rate also would be increased.

In these studies, we fasted rats overnight, and the next morning, at the beginning of the daily light period, fasted them or gave them free access to a protein-free meal or a meal containing 400 g casein/kg diet. Retinas were removed 2 h later. The protein meal caused retinal tyrosine levels to rise by 2.5-fold (Table 2), and tyrosine hydroxylation rate almost doubled. This effect was not due simply to the ingestion of any food, since when rats ingested a non-protein, carbohydrate meal, no increases in retinal tyrosine level or hydroxylation rate occurred (Table 2; Fernstrom & Fernstrom, 1987). Similar studies conducted by others affirmed this effect, showing overall DA synthesis to be stimulated by this treatment (Gibson, 1986).

Given that the meal-induced increments in retinal tyrosine levels are as large as those produced by injecting large doses of tyrosine (Fernstrom *et al.* 1986b), and that tyrosine

Table 2. *Effects of ingesting single meals on tyrosine levels and hydroxylation rate in the light-exposed rat retina* (From Fernstrom & Fernstrom, 1987)

(Mean values with their standard errors. Groups of rats, fasted overnight, were given free access the next morning to either nothing, a meal containing 400 g casein/kg (dry weight), or a protein-free meal (CHO meal). After 90 min, the food was removed, and all animals received NSD-1015 (100 mg/kg intraperitoneally) and were killed after 30 min)

Treatment	Serum tyrosine (nmol/ml)		Serum tyrosine:total LNAA ratio		Retinal tyrosine (nmol/mg protein)		Retina DOPA synthesis (ng/mg protein)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Fasting	76	5	0.24	0.01	1.85	0.10	1.27	0.10
CHO meal	68	4	0.23	0.01	1.93	0.16	1.86	0.42
Protein meal	293**	20	0.37**	0.02	4.17**	0.13	2.51*	0.32

LNAA, large neutral amino acids; DOPA, dihydroxyphenylalanine.

Mean values were significantly different from fasting values (Newman-Keuls test): * $P < 0.05$, ** $P < 0.01$.

injection is known to stimulate DA synthesis in brain (Wurtman *et al.* 1980; Fernstrom, 1983), we concluded that single protein meals probably also stimulate DA synthesis in brain neurons. However, the condition for such an effect would be that the neurons must be active, which excludes certain groups of brain DA neurons, like those projecting from the *substantia nigra* to the *corpus striatum* (Scally *et al.* 1977; Fernstrom *et al.* 1986b), which fire at a slow rate (these neurons are participants in the extrapyramidal motor system, which controls posture and muscle tone). One group of DA neurons in the hypothalamus (those controlling pituitary prolactin secretion) also appears unresponsive to tyrosine and, thus, probably fires at a slow rate. Presumably, these also would be unresponsive to meal-induced increases in local tyrosine levels. In contrast, DA synthesis in the DA neurons projecting from the midbrain to the prefrontal cortex (Bannon & Roth, 1983), which appear always to be firing at a rapid rate, might be responsive to protein meals. At present, no studies have looked for subpopulations of brain DA (or other catecholamine-synthesizing) neurons that might exhibit increases in tyrosine level and hydroxylation rate in response to the ingestion of protein meals. Such a study should be undertaken, since the identification of responsive subgroups of neurons may reveal the physiological importance of this biochemical relationship. For example, as described later, if hypothalamic DA neurons involved in appetite regulation were responsive, the result would suggest that the connection between food intake and CNS tyrosine levels and DA synthesis might provide appetite-regulating circuits with information regarding recent protein intake. Hypothalamic, noradrenaline-synthesizing neurons involved in appetite circuits that are responsive to local tyrosine increases might also be involved.

Recently, we observed an additional relationship between food ingestion and catecholamine synthesis. In these experiments, we have examined the effects of chronic variations in protein intake on CNS tyrosine levels and hydroxylation rate. These studies were based on earlier work showing that the ingestion for 1–2 weeks of a diet containing different levels of protein produced dose-related differences in CNS tyrosine levels. In particular, brain tyrosine levels were lowest when rats consumed diets containing 0–20 g protein/kg, rose progressively as the protein content was increased to 50 and 100 g/kg, and then plateaued (Table 3; Peters & Harper, 1985; Gustafson *et al.* 1986). The range

Table 3. *Serum tyrosine:LNAA and brain tyrosine concentrations in rats fed on different levels of dietary protein (casein)* (Adapted from Gustafson *et al.* 1986)

(Mean values with their standard errors. Groups of six male rats consumed one of the experimental diets *ad lib.* for 14 d, and were then killed during the day)

Dietary protein content (g casein/kg)	Serum tyrosine:total LNAA	Brain tyrosine (nmol/g)	
		Mean	SE
0	0.09	94	40
2	0.10	105	43
5	0.13	157	24
10	0.24	251	55
15	0.22	251	69
21	0.17	221	55

LNAA, large neutral amino acids.

Table 4. *Effect of chronic protein ingestion on retinal tyrosine levels and tyrosine hydroxylation rate* (M. H. Fernstrom and J. D. Fernstrom, unpublished results)

(Mean values with their standard errors. Groups of six male rats ingested for 14 d a diet containing either 0, 20, 50, 100 or 200 g casein/kg. They then received NSD 1015, an inhibitor of aromatic-L-amino acid decarboxylase (EC 4.1.1.28), 2 h into the normal daily dark period, and were killed 30 min later. Lights remained on during the final 2.5 h period)

Dietary group (g protein/kg)	Retinal tyrosine (nmol/mg protein)		Retinal DOPA (ng/mg protein)	
	Mean	SE	Mean	SE
20	0.93*	0.03	1.18**	0.15
50	2.58	0.48	1.60	0.05
100	3.72	0.51	1.88	0.13
200	3.67	0.52	2.13	0.32

*F=6.56, $P<0.01$, **F=3.75, $P<0.05$ (one-way ANOVA).

of tyrosine concentration between the lowest and highest points was found to be 2–2.5-fold, a difference that in single-meal studies is associated with clear changes in tyrosine hydroxylation rate and DA synthesis (Fernstrom *et al.* 1986b; Gibson, 1986; Fernstrom & Fernstrom, 1987).

Accordingly, we examined whether we could cause CNS tyrosine hydroxylation rate to vary predictably by altering chronic dietary protein intake. The results were unambiguous. Groups of rats ingested 20, 50, 100 or 200 g casein/kg diets for 2 weeks, and were killed 2.5 h into the daily dark period of the 14th day (lights left on; the rats received the drug, NSD-1015, 30 min before death to block decarboxylation of DOPA). Tyrosine levels in retina showed the anticipated effects; they were low in rats ingesting 20 g protein/kg, and rose progressively in rats ingesting 50 and 100 g protein/kg to a plateau; tyrosine hydroxylation rate was observed to follow tyrosine levels (Table 4). Thus, the retinal DA neurons responded as clearly to chronic changes in tyrosine availability as they did to acute changes. We also wondered if such diet-induced alterations in tyrosine level and hydroxylation rate might also occur in a CNS region known to be involved in food intake regulation, i.e. the hypothalamus (Hoebel & Leibowitz, 1981; Wellman, 1992; Wellman *et al.* 1993). Given the similarity in LNAA transport mechanisms across blood–brain and blood–retina barriers, similar effects on tyrosine levels might be anticipated. But we did not know in advance whether catecholamine neurons in hypothalamus would be active, that is whether or not hypothalamic tyrosine hydroxylase would be responsive to changes in tyrosine level. Thus, it was of great interest to find that, just as in retina, hypothalamic tyrosine levels and hydroxylation rate increased substantially as dietary protein content increased from 20 to 100 g/kg (Fernstrom & Fernstrom, 1994). At present, because we measure tyrosine hydroxylation rate, we cannot conclude for hypothalamus which catecholamines have been affected. Unlike the retina, which contains primarily DA neurons, the hypothalamus contains large numbers of both DA and noradrenaline nerve terminals; since tyrosine hydroxylation occurs in both places, the synthesis of either or both catecholamines may have been stimulated. However, studies are currently being conducted to identify which catecholamine-containing neurons in hypothalamus are responsive.

DIET, TYROSINE LEVELS AND CATECHOLAMINE SYNTHESIS: POSSIBLE
ROLE OF APPETITE REGULATION

The previously mentioned findings show that for some CNS neurons, tyrosine levels and catecholamine synthesis are metabolically linked to the amount of protein ingested in the diet. It is unclear functionally why retinal DA neurons should show this relationship. We originally chose retinal DA neurons as a model system for examining the relationship between tyrosine level and DA synthesis, since we could activate tyrosine hydroxylase in these neurons physiologically (by light). We did not expect to find an effect of dietary protein and, thus, must ponder the existence of this particular relationship. However, for hypothalamic catecholamine neurons, which have been linked to food intake and appetite regulation for several decades (Hoebel & Leibowitz, 1981; Wellman, 1992; Wellman *et al.* 1993), the existence of the same relationship suggests it might serve as a biochemical link informing the hypothalamus about protein intake. This possibility has appeal. Animals (here, the rat) have an absolute protein requirement (National Academy of Sciences, 1978). Presumably, they somehow sense their level of protein intake (Ashley, 1985), in order to keep up with metabolic demands. Perhaps they do so insensibly via changes in tyrosine level and catecholamine synthesis. When protein intake is at or above requirement levels (100–120 g/kg diet in growing rats; >60 g/kg diet in adult rats; National Academy of Sciences, 1978), CNS tyrosine levels and catecholamine synthesis should be at an upper plateau. Based on data like those in Tables 3 and 4, as protein intake falls below requirement levels tyrosine levels and catecholamine synthesis should fall. Since both catecholamine synthesis and release are affected by changes in tyrosine levels (Sved *et al.* 1979a,b; During *et al.* 1988), such reduction should lead to reduced catecholamine release, which presumably would affect the functioning of brain circuits in which they participate. In the hypothalamus some such circuits are involved in food intake regulation (Hoebel & Leibowitz, 1981) and, perhaps, protein intake regulation and, thus, might be influenced. Such effects might form the basis for initiating a change in behaviour. In this case, the reduced catecholamine signal might lead to increased appetite for protein-containing foods. Certainly, rats expend effort to maintain protein adequacy when they must work to obtain protein (Ashley, 1985). Perhaps the relationship between dietary protein intake and tyrosine levels and catecholamine synthesis is the link between how much protein is ingested and the animal's ultimate desire to maintain adequate protein intake.

Finally, an interesting example is found in nature that illustrates how the brain might use these biochemical–metabolic relationships to aid in the detection of protein intake, both acutely and chronically. Acutely, many non-human primates show a characteristic diurnal pattern of food intake in the wild. Following their overnight sleeping period, they begin the day by ingesting fruit, which contains carbohydrates, little protein, and usually very little fat (Rogers *et al.* 1990); later in the day, they shift their food selection to predominantly leaves and shoots, their primary sources of protein (Raemaekers, 1978; Gaulin & Gaulin, 1982; Marriott, 1988). This natural diurnal pattern of food intake is interesting, because it sets up a metabolic pattern that should cause CNS catecholamine synthesis and release to be a sensitive indicator of diurnal protein intake. Brain tyrosine uptake and catecholamine synthesis should be low early in the day (because of fruit (carbohydrate) ingestion, which does not alter them), and then rise through the remainder of the day (because the animal shifts to protein-containing food sources, which raises them). Based on the studies in rats, one might reasonably speculate that the

rate of increase in CNS tyrosine and catecholamines in the afternoon might even depend on the richness of the protein sources the animals locate and ingest; if they find protein sources that are low in protein, the increase in tyrosine might not be as rapid as after they ingest foods containing higher amounts of protein. Such a system, if the brain (hypothalamus) used it to monitor protein intake, could very well be employed to identify when sufficient protein has been consumed for the day. Monkeys in the wild do not seem to have excess protein in their diet; they may often find themselves at or below requirement levels (Milton, 1979; Nakagawa, 1989), making the sensing of protein intake a matter of some nutritional importance.

Monkeys in the wild might also benefit from the relationship between chronic protein intake and CNS tyrosine levels and catecholamine synthesis. If protein intake is often marginal, then the provision of data to the brain indicating the animal's success in meeting its longer-term protein needs might be of value in determining how much to motivate protein-seeking behaviour from day-to-day. Because of the importance of achieving dietary protein adequacy, the existence of multiple mechanisms for monitoring both acute and chronic protein intake should not be considered surprising.

Humans pose a more difficult problem. Mechanisms for protein intake regulation, like those discussed previously, may exist in this species. However, because they may operate at about protein requirement levels, and individuals in developed countries typically exceed daily protein requirements by a considerable amount, they may not easily be discernible. Thus, it may be necessary to examine this relationship in a population whose diet has a much lower protein content than that commonly found in developed countries.

We hope at least to examine this issue in primate models in the next few years. The ultimate goal is to gain an insight into metabolic mechanisms that influence food selection in humans. The bases for selecting the primate for study are that a significant body of evidence exists regarding their food intake habits in their natural habitats, and that humans and monkeys derive from a common ancestry and, thus, a common dietary history (Milton, 1993). Understanding mechanisms of food-intake monitoring and food choice in non-human primates (and other animals), therefore, should aid the elucidation of similar mechanisms in humans.

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