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Use of Tyrosine and Other Nutrients to Enhance and Sustain Performance

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Summary

Administration of supplemental tyrosine can increase the release of the catecholamines dopamine, norepinephrine, and epinephrine from physiologically-active neurons, and can thereby modify behaviors and other neuronal functions (e.g., control of blood pressure; neuroendocrine secretion) that are mediated by these neurotransmitters. The tyrosine acts by increasing the substrate-saturation of the enzyme tyrosine hydroxylase; when a given neuron is firing frequently this enzyme becomes phosphorylated and, consequently, tyrosine-dependent. The amount of tyrosine that enters the brain varies with the plasma tyrosine ratio, i.e., the ratio of the plasma tyrosine concentration to the summed concentrations of other large neutral amino acids that compete with tyrosine for transport across the blood-brain barrier. Hence, the administration of pure tyrosine is much more effective than eating proteins, which contain tyrosine - and deliver to the blood stream - considerably larger amounts of the other large neutral amino acids. Tyrosine administration protects rats from the neurochemical and behavioral effects of stress; its ability to enhance performance of stressed humans is under exploration.

Our studies on the use of tyrosine and other nutrients to modify neurotransmitter synthesis and thereby affect behavior grew out of a research program started at MIT about a decade ago, dealing broadly with the effects of nutritional and metabolic factors on the brain and behavior. Initially, we showed that the rates at which the serotonin-releasing neurons in rat brain synthesize and release that neurotransmitter depend on brain levels of tryptophan (serotonin's amino acid precursor) [1,2,3]; thus serotonin-mediated neurotransmission was increased after animals received tryptophan, and could be increased or decreased after they consumed meals that modified the pattern of amino acids in the plasma. For example, if fasting rats were given a carbohydrate-rich, protein-poor meal, plasma levels of the large neutral amino acids (LNAA) other than tryptophan declined markedly because of the insulin secreted by the carbohydrate; as a consequence, the competition between these compounds and tryptophan for blood-brain barrier transport sites lessened, and more tryptophan entered the brain [4,5,6]. In contrast, consumption of a protein-rich meal selectively elevated plasma levels of the competing LNAA, thus diminishing brain tryptophan and slowing serotonin synthesis [5]. We subsequently affirmed that: a) food or tryptophan consumption causes the same plasma changes in humans as in rats [7] - and thus probably the same changes in brain serotonin; b) the effect of any tryptophan dose on the brain can be enhanced by giving it along with a carbohydrate, because of the resulting fall in blood LNAA; c) the increase in serotonin synthesis occurring when brain tryptophan levels rise is more-or-less independent of the firing frequency of the serotoninergic neurons [3]; and, d) food-induced changes in brain serotonin synthesis are associated with changes in physiological and behavioral functions thought to involve this transmitter (like pain sensitivity; sleepiness; appetite for carbohydrates; blood pressure; and the secretion of certain pituitary hormones [3,8,9]).

Subsequently, we observed that the syntheses of other neurotransmitters could also be affected by changing brain levels of their precursors: Giving choline (or oral lecithin, which dissociates to choline) could, under appropriate conditions, enhance acetylcholine synthesis [10,11] and release [12,13,14], while tyrosine administration could similarly affect the production of catecholamines, both in the brain [15,16] and in sympathoadrenal cells [17]. However, whereas tryptophan administration in physiologic doses (i.e., doses that kept plasma and brain tryptophan within their normal ranges) always accelerated serotonin synthesis, giving choline or tyrosine affected acetylcholine or catecholamine synthesis only when particular neurons happened to be firing frequently (that is, only when these neurons were physiologically active) [3]. This coupling has important physiological consequences: it apparently allows the brain to "choose" which particular catecholaminergic neurons will be "allowed" to respond - when subjects receive tyrosine or choline, or when they consume a meal that raises brain levels of these nutrients: If the quantity of catecholamine or acetylcholine being released from a particular set of neurons is sufficient for the brain's purposes, those neurons can, by slowing their rate of firing, protect themselves from changes in their outputs that would otherwise follow when plasma composition changes. A corollary of this relationship is that tyrosine or choline can, at least theoretically, be used to enhance neurotransmission, locally, in a disease state or when such transmission is inadequate for the body's needs (i.e., during prolonged stress or prolonged periods when focussed attention is required), without risk of severe side-effects. Of course, this corollary requires confirmation by experimental testing in each situation in which the precursor is proposed for use.

Some of the evidence supporting the conclusion that tyrosine-responsiveness is coupled to neuronal firing frequency follows:

1. Giving rats doses of tyrosine sufficient to double brain tyrosine levels failed to enhance the release of dopamine from nigro-striatal neurons (as assessed by measuring striatal levels of the dopamine metabolites DOPAC and HVA) in control animals, but caused major increases in dopamine release when animals were pretreated with:

a) haloperidol, a drug that blocks dopamine receptors, impairing synaptic transmission and thus accelerating nigro-striatal firing [16];

b) reserpine which depletes neuronal dopamine, thereby also impairing neurotransmission and secondarily accelerating nigro-striatal firing [18];

c) gamma-butyrolactone - which suppresses nigro-striatal firing, blocking the release of dopamine into synapses, thus blocking the activation of presynaptic dopamine receptors which normally diminish dopamine release [18]. (Like the above treatments, this drug activates the enzyme - tyrosine hydroxylase - that controls dopamine synthesis.)

d) chemical lesions destroying 75% or more of the neurons [19]. This treatment causes the surviving neurons to fire more frequently, thereby becoming tyrosine-responsive.

2. Tyrosine administration increases dopamine release from retinal amacrine cells when these cells are activated by exposing animals to light but not among rats kept in darkness -- even though retinal tyrosine cells rise by at least as much [19a].

3. Giving rats (or people) tyrosine can either raise blood pressure [20], lower it [21], or fail to affect it at all - depending on what the blood pressure happens to be at the time the tyrosine is administered (and which catecholaminergic neurons happen to be firing.) In hypertensive rats, the brain - in an effort to diminish blood pressure - activates norepinephrine-releasing neurons in the brain stem, causing, "downstream," a reduction in sympatho-adrenal firing. Hence, the brain stem neurons are responsive to tyrosine (because they are firing frequently); its administration causes them to make and release more norepinephrine (manifest as an increase in the levels of norepinephrine's metabolite MHPG-sulfate within the brain stem), thereby lowering blood pressure (18). In contrast, in hypotensive rats (made hypotensive by hemorrhagic shock), brain stem noradrenergic neurons are relatively inactive, and the sympathoadrenal neurons very active; now it is the latter neurons that respond to the tyrosine, making more norepinephrine and epinephrine, and raising blood pressure back to normal (20). It seems very useful that the system shuts itself off, as it were, terminating its response to tyrosine when blood pressure has returned to the desired range. (As described below, we have obtained additional evidence that tyrosine's ability to raise blood pressure in animals suffering from hemorrhagic shock results from an increase in peripheral, sympathoadrenal catecholamine synthesis: tyrosine's action in such animals is blocked by i) adrenalectomy; ii) pretreatment with carbidopa - which blocks amino acid decarboxylation in peripheral tissues but not in the brain -; and iii) pretreatment with phentolamine, a drug that blocks peripheral but not CNS alpha receptors. The anti-shock action of tyrosine is unrelated to the formation of tyramine [21A].)

Abundant additional evidence exists for the relationship between neuronal firing frequency and tyrosine-responsiveness, and tyrosine is currently being examined for possible use in such "catecholamine-deficiency" diseases as Parkinson's disease [22] and depression [23]. To our knowledge, every publication that has tested this relationship has confirmed it [e.g., 3,24,25].

At first we believed that the most probable mechanism that caused frequently-firing catecholaminergic neurons to become tyrosine-responsive had to do with the kinetics of the enzyme tyrosine hydroxylase. This enzyme does become activated when neurons containing it fire: One, two, or three of its amino acid residues become phosphorylated, changing its allosteric structure and very markedly enhancing its affinity for its tetrahydrobiopterin cofactor [26]. In its basal state, the enzyme is very poorly saturated with the cofactor, so that cofactor levels limit its overall activity. (It is also subject to considerable end-product inhibition by various catechols - which act to limit cofactor saturation.) Once phosphorylated, the enzyme becomes much more saturated with cofactor, and thus much more influenced by its relative unsaturation with tyrosine, - whose levels in brain are on the same order as the enzyme's Km, a range in which the enzyme would be expected to be most sensitive to small changes in tyrosine levels. The phosphorylation is reversible: When the neuron slows its firing, the enzyme becomes dephosphorylated, once again becoming limited by cofactor saturation [27]. However, we now have evidence that an additional mechanism, the depletion of tyrosine within catecholaminergic nerve terminals, may be just as important in allowing tyrosine administration to enhance catecholamine release [27a]. Tyrosine administration may "protect" against the reduction in transmitter release (from catecholaminergic neurons) that would otherwise occur with continuous firing, by keeping intraneuronal tyrosine levels from falling.

Tyrosine is a naturally-occurring amino acid. While it is possible to induce tyrosine toxicity experimentally (by giving animals massive tyrosine doses, and concurrently depriving them of adequate protein) [28], available evidence indicates that small, supplemental tyrosine doses are readily tolerated without side-effects by humans. If this tyrosine can amplify catecholamine release when such an amplification is desirable - for example, to sustain performance and the ability to cope when the locus coeruleus has been depleted of its norepinephrine in prolonged stress situations - it may have considerable utility. Some of the studies proposed below will examine the effects of various tyrosine doses on normal volunteers.

Rigorous testing of the possibly-beneficial effects of tyrosine on human performance is in its infancy; a description of published studies relating to these effects is provided in another paper presented at this symposium. It might be anticipated - on the basis of the animal studies described above - that tyrosine would do very little in normal people exposed to normal (i.e., non-stressful) environments, but might be quite effective in helping people sustain optimal performance when they are subjected to major and continuing demands. Future testing should tell.

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Discussion

Vogt, GE

What would you recommend for a pilot that has to work for 28 or 32 hours continuous operations?

Wurtman, US

My comments are not on pilots in similar circumstances but on people who were put under stress and in that circumstance I believe that subjects received 100 mg/kg. Now, the reason for using that dose is simply that everyone has always used that dose. That was the dose that was used on rats, 100mgm/kg, and so that dose was used on people. By the way, it does double the ration of plasma tyrosine to the competitors. The point is, we don't know where we are on the dose/response curve. It may be that lower doses will be equally effective or it may be that much higher doses would be far more effective. And I think it is important that dose/response studies be done. Also, it is terribly important to know what else the person is eating. If you give the tyrosine along with a piece of meat you will have so much leucine, isoleucine and valine it will block the uptake of tyrosine into the brain. On the other hand, if you give it with carbohydrate, starch or sugar, it doesn't matter, you will potentiate the effect on the brain. The important thing is to standardize in your experiments what the person is digesting when you give them the tyrosine. Well, again Dr. Banderet will be talking about their data and I believe those were single dose studies. If you are going to do studies of this sort, it is a very good idea to make a collaboration with a biochemist, perhaps you are one yourself, so that you can monitor, in a few subjects, the plasma tyrosine levels and the plasma tyrosine ratios. If you give the kind of dose they gave this will elevate the ratio for four or five hours and that's an adequate window for their experiments. But the field is in its infancy and I think such questions as dose and duration, I am sure will be worked out, but really must be worked out.

Von Restorff, GE

What was the dose of tyrosine you used and how often did you give that dose daily?

Banderet, US

In the recent study done by Banderet, Lieberman, et.al. it was a total dose of 100 mg/kg given in two divided doses about 50 minutes apart. This total dose was given previously in rat studies; it worked so we used it. Tyrosine has also been given to depressed patients in larger doses. References are given in Banderet et.al. paper.