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Review

Behavioral and cognitive effects of tyrosine intake in healthy human adults

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ABSTRACT

The amino acid tyrosine is the precursor to the catecholamine neurotransmitters dopamine and norepinephrine. Increasing tyrosine uptake may positively influence catecholamine-related psychological functioning. We conducted a systematic review to examine the effects of tyrosine on behavior and cognition. Fifteen studies were reviewed. All studies except one involved tyrosine loading during a single test session. In most behavioral studies, there were no significant effects of tyrosine on exercise performance. In contrast, cognitive studies employing neuropsychological measures found that tyrosine loading acutely counteracts decrements in working memory and information processing that are induced by demanding situational conditions such as extreme weather or cognitive load. The buffering effects of tyrosine on cognition may be explained by tyrosine's ability to neutralize depleted brain catecholamine levels. There is evidence that tyrosine may benefit healthy individuals exposed to demanding situational conditions. For future research we recommend moving from studying the acute effects of a single tyrosine load in small samples to studying the behavioral and cognitive effects of tyrosine in larger groups over multiple weeks.

Contents

1. Introduction

In recent years, nutrition science has been gaining influence on hobby athletes and people concerned with an effective diet, as they have increasingly focused on nutritional factors to augment their personal performance and well-being. This has led the dietary supplement industry to grow, and offer various products designed to improve physical and mental performance (Bucci and Unlu, 2000). For example, interest in protein mixtures has increased, particularly thanks to the ability of whey protein to support gains in lean muscle mass after exercise (Volek et al., 2013). These muscular gains can improve performance in sports, and in occupations that demand strength.

Supplement producers have also been marketing products that contain specific amino acids, either added to whey protein mixtures or in isolation (Bucci and Unlu, 2000). Amino acids are the building blocks

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of proteins. Some amino acids also act as neurotransmitter precursors, meaning that certain neurotransmitters are directly or indirectly synthesized from specific amino acids (Young, 1996). Altering the intake of these amino acids may influence the function of their respective neurotransmitters. At the blood–brain barrier, many amino acids compete for uptake into the brain. For these amino acids, the effect of a specific amino acid supplement on brain function may be more predictable than the effect of a supplement containing a mixture of different amino acids (Strüder et al., 1998). One relevant neurotransmitter precursor is the amino acid L-tyrosine (tyrosine from here onwards). A 1996 review on dietary neurotransmitter precursors reported beneficial effects of tyrosine on cognitive task performance, fatigue, and general alertness under various stressful conditions (Young, 1996). There were no consistent effects on mood, although some case reports and small studies suggested that tyrosine might potentiate the action of antidepressant drugs. The present review integrates all placebo-controlled studies on the effects of tyrosine intake on behavior and cognitive (i.e., neuropsychological) task performance, most of which were published after 1996.

Increased tyrosine intake has the potential to influence the catecholamine neurotransmitters dopamine and norepinephrine via its conversion into L-3,4-dihydroxyphenylalanine (L-DOPA), the direct precursor to dopamine, which in turn gets converted to norepinephrine (Fernstrom and Fernstrom, 2007). Tyrosine hydroxylase, the enzyme involved in the conversion from tyrosine to L-DOPA, is about 75% saturated with tyrosine under typical physiological conditions (Carlsson and Lindqvist, 1978). As the other enzymes involved in catecholamine synthesis have low saturation rates, there is a modest but significant potential to increase brain catecholamine synthesis by increasing local tyrosine levels. This brings the question whether increased tyrosine intake can have significant effects on human behavior and cognition.

The most commonly adopted hypothesis about stress-induced performance decrements holds that reduced brain catecholamine levels account for this phenomenon (O'Brien et al., 2007; Colzato et al., 2013). In line with this, tyrosine depletion experiments, in which participants consume an amino acid mixture devoid of tyrosine and its precursor, phenylalanine, suggest that acute reductions in brain catecholamine levels lead people to behave in a less motivated way (McLean et al., 2004; Roiser et al., 2005; Cawley et al., 2013) or develop cognitive impairments (Harmer et al., 2001). Moreover, reduced brain catecholamine levels seem to make mood more vulnerable to the negative effects of low light exposure (Cawley et al., 2013). Consequently, positive effects of increased tyrosine intake in demanding situations could be explained by the replenishment of brain catecholamines.

In short, selective increases in the intake of tyrosine may benefit those aspects of human behavior and cognition that are under the catecholaminergic control (Young, 1996). To test this idea further, we systematically reviewed tyrosine administration studies conducted in healthy human adults. Our main research question was which aspects of human behavior and cognition improve following increased tyrosine intake. Given the above, these would be expected to include alterations in behavioral and cognitive responses to physical and mental stressors. Beneficial effects of tyrosine could be relevant for a range of target populations, including sportsmen, university students, manual laborers, office workers, and patients with psychological problems.

2. Materials and methods

The search for and selection of relevant studies was conducted in the electronic databases MEDLINE and PsycINFO according to the PRISMA guidelines for systematic reviews (Liberati et al., 2009). We entered ("tyrosine" AND "load*" OR "supplement*") into the search field. To be selected by the first two authors (AH and SEJ), a study needed to be published in an academic journal and have used a placebo-controlled experimental design with healthy human adults that involved single or multiple dosing with tyrosine in one day (loading) or repeated dosing over multiple days (supplementation). Studies in which tyrosine was mixed with other compounds of experimental interest were excluded, because our objective was to examine the effects of increased tyrosine intake in isolation.

3. Results

The search, last conducted in November 2014, yielded 3059 results. The first two authors (AH and SEJ) then selected 72 studies that met the selection criteria based on the title. In the next step, they independently read the abstracts of these studies and considered whether they should remain included based on the information in the abstract. In the final step, they retrieved full-text versions of the 17 remaining studies and determined whether appropriate methods were used. One study was then excluded based on the full text because it had tested the effects of a mixture with various amino acids yet labeled it as a tyrosine intervention in title and abstract. Another study was excluded because it used a non-experimental design without adult participants.

Characteristics and main outcomes of the 15 reviewed studies are presented in Table 1. Ten studies involved a single tyrosine load, three studies involved two loads in one day, and one study involved two loads in the hour prior to testing and additional loads every 10 min during the 1.5-hour experiment (on average 8 loads). One study supplemented tyrosine daily for 3–4 months.

Dosages of tyrosine also varied across studies. Six studies involved fixed amounts of tyrosine, ranging from 2 to 20 g. The remaining nine studies used a dosage adjusted to the body weight of the participants, ranging from 25 to 150 mg/kg. Some studies administered tyrosine in solid form, namely in a nutrient bar (O'Brien et al., 2007; Mahoney et al., 2007; Kishore et al., 2013) or in apple sauce (Thomas et al., 1999; Sutton et al., 2005; Palinkas et al., 2007; Shurtleff et al., 1994). The remaining studies offered tyrosine in water (Strüder et al., 1998; Chinevere et al., 2002; Tumilty et al., 2011, 2014), orange juice (Colzato et al., 2013, in press), or a sugar-free fruit drink (Watson et al., 2012).

All seven studies in which plasma tyrosine levels were measured (Strüder et al., 1998; Sutton et al., 2005; Shurtleff et al., 1994; Chinevere et al., 2002; Tumilty et al., 2011, 2014; Watson et al., 2012) found these levels to be significantly elevated after tyrosine intake compared to placebo. All studies were placebo-controlled and conducted under double-blind conditions. In most studies, the food or drink in the placebo condition contained no protein. In one study, the placebo was an isocaloric whey protein drink, which means it contained some tyrosine, though less than the amount of tyrosine in the active condition (Tumilty et al., 2014). All studies except one (Palinkas et al., 2007) used a within-subjects design with a counterbalanced treatment order.

3.1. Behavioral effects

While one study found tyrosine to enhance endurance exercise performance (Tumilty et al., 2011), five studies found no significant differences between tyrosine and the placebo (Strüder et al., 1998; Sutton et al., 2005; Chinevere et al., 2002; Tumilty et al., 2014; Watson et al., 2012). All six studies involved physically trained young men in sample sizes ranging from 7 to 20 participants. Two studies operationalized endurance exercise performance as the time spent on a cycling time trial, three studies operationalized it as the time cycled until exhaustion, and one study operationalized it as the time spent on a treadmill until exhaustion. Three studies investigated endurance exercise performance in a warm environment and the other three used normal temperatures. The study in which participants performed better on tyrosine than on placebo was similar in methodology to the other five behavioral studies.

Table 1
Overview of included studies.

Reference	N	Dosage	Population	Mean age (years)	Placebo	Design	Main outcome measures	Results	Effect sizes (d)
One-time loading									
8	22	2.0 g	Healthy female undergraduate students	19.7	Cellulose	W (DB, RCD)	N-back task:		
							– RT	– Decreased	– −1.12
							– Misses	– Decreased	– −1.00
							– Hits	– Increased	−+1.00
15	10	6.5 g	Male Indian army soldiers	Unknown	Tyrosine-free nutrient bar	W (DB, RCD)	– RT	– Heat-induced increase prevented	Unknown
							– P300 latency	– Heat-induced increase prevented	
							– P300 amplitude	– No change	
							– M100 latency	– Heat-induced increase prevented	
							– M100 amplitude	– Heat-induced decrease prevented	
							– Plasma catecholamines	– Increase	
16	20	11.3 g	Duty personnel and government civilians	28.8	Cellulose	W (DB, RCD)	– Working memory accuracy	– Increased	Unknown
							– Arithmetic skills	– Not significantly affected	
17	20	12.2 g	Healthy men	32	Cellulose	W (DB, RCD)	– Time until exhaustion on treadmill	– Not significantly affected	Unknown
							– Plasma tyrosine	– Increased	
							– Plasma norepinephrine	– Not significantly affected	
19	8	12.4 g	Healthy men	27.5	Cellulose	W (DB, RCD)	– Match-To-Sample accuracy	– Cold-induced decrease in performance prevented	– Unknown
20	9	1.8 g	Male competitive cyclists	25	Sweetened water	W (DB, RCD)	Time required for time trial task on a cycling ergometer	Not significantly affected	−0.21
21	7	11.7 g	Endurance-trained men	Median = 20	Isocaloric whey protein drink	W (DB, RCD)	– Cycling time trial duration	– Not significantly affected	– −0.05
							– Power output	– Not significantly affected	– Unknown
22	8	11.3 g	Moderately trained men	32	Tap water	W (DB, RCD)	– Time until exhaustion on cycling ergometer	– Increased	Unknown
							– Rating of perceived exertion	– Not significantly affected	
23	22	2.0 g	Healthy women	20.4	Cellulose	W (DB, RCD)	– Response inhibition RT	– Decreased	– 1.05
							– Response execution RT	– Not significantly affected	– Unknown
24	32	2.0 g	Healthy adults	19.4	Cellulose	W (DB, RCD)	– Divergent thinking	– Not significantly affected	– $d = 0.50$
							– Convergent thinking	– Increased	– Unknown
Two-time loading									
4	10	20.0 g (1.25 h apart)	Endurance-trained male cyclists	25.5	Unknown	W (DB, RCD)	– Time until exhaustion on an ergometer	– Not significantly affected	Unknown
							– Plasma prolactin	– Increased	
7	15	11.4 g (~4 h apart)	US army enlisted soldiers	20	Tyrosine-free nutrient bar	W (DB, RCD)	– Match-to-Sample accuracy	– Cold-induced decrease in performance prevented	Unknown
							– Marksmanship accuracy	– Cold-induced decrease in performance prevented	
14	19	11.6 g (>2 h apart)	US army enlisted soldiers	20.5	Tyrosine-free nutrient bar	W (DB, RCD)	– Match-to-Sample accuracy	– Cold-induced decrease in performance prevented	Unknown
							– Match-to-Sample study time	– Cold-induced decrease in performance prevented	
Multiple loadings									
25	8	12.0 g (total amount)	Trained young men	23	Sugar-free fruit drink	W (DB, RCD)	– Time until exhaustion on a cycling ergometer	– Not significantly affected	Unknown
							– Rating of perceived exertion	– Not significantly affected	
Long-term supplementation									
18	65	12.0 g	Antarctic research station inhabitants	36.8	Cellulose	B (RCT, longitudinal design)	– Norepinephrine	– Decreased more (winter); decreased less (summer)	Unknown
							– Free T3	– Increased (during summer)	
							– Global Mood Score	– Increased (during winter)	
							– Serum TSH	– Decreased	

Study characteristics and main outcomes.
Abbreviations: W = within-subjects, B = between-subjects, DB = double-blind, RCD = randomized crossover design, RCT = randomized clinical trial, RT = reaction time.

3.2. Cognitive effects

The most commonly reported effect, observed in five studies, was that tyrosine prevented decrements in cognitive task performance under physically or mentally tasking conditions. Three of these studies observed superior scores of the tyrosine group on tests of working memory under physical stress as elicited by exposure to cold temperatures (O'Brien et al., 2007; Mahoney et al., 2007; Shurtleff et al., 1994). The other two studies observed higher scores of the tyrosine group on working memory tasks that require multitasking (Colzato et al., 2013; Thomas et al., 1999).

Three further studies reported other cognitive benefits. Tyrosine reduced response inhibition reaction times in one study (Tumilty et al., 2011). In another study, tyrosine prevented heat-induced increases in reaction times (Kishore et al., 2013). This study also included EEG measures and reported that the observed cognitive effect of tyrosine might be explained by preventing heat-induced increases in P300 latencies, assessed using an auditory odd-ball paradigm (Kishore et al., 2013). The P300 is thought to represent information processing, working memory, and stimulus categorization. The P300 latency can be interpreted as an index of the efficiency with which novel stimuli are evaluated.

In a final study, tyrosine improved convergent thinking as measured by a cognitive task which required participants to find a common associate for three seemingly unrelated words (Colzato et al., 2014). Convergent thinking was defined as the top-down controlled process of coming up, in response to multiple given problems, with a single solution.

3.3. Emotional effects

Our literature search yielded only one study which involved repeated tyrosine dosing over multiple days (Palinkas et al., 2007). This tyrosine supplementation study, conducted in Antarctica in two seasons, was also the only reviewed study to examine tyrosine's effects on mood. Over the course of the Antarctic winter, tyrosine increased global mood scores from baseline by 47%, whereas in the placebo condition global mood scores decreased by 136%. During the summer, there were no significant changes in mood.

3.4. Biological effects

Two studies have reported tyrosine-induced changes in peripheral neurotransmitter levels. In the Antarctica study, plasma norepinephrine levels declined more in the tyrosine group than in the placebo group during the winter. However, plasma norepinephrine levels declined less in the tyrosine group than in the placebo group during the summer (Palinkas et al., 2007). Another study reported an acute tyrosine-induced increase in plasma norepinephrine levels, compared to no change in the placebo condition (Kishore et al., 2013).

Two studies reported tyrosine-induced hormonal changes. The Antarctica study reported lower serum thyroid-stimulating hormone and higher plasma free triiodothyronine levels as a result of tyrosine supplementation during the winter season, with no effects during the summer (Palinkas et al., 2007). The other study observed acute tyrosine-induced elevations in prolactin during exercise (Strüder et al., 1998).

4. Discussion

Increased tyrosine intake has various potential uses. We found that tyrosine is able to combat the decrements in working memory, slowed information processing, and worsening of mood that might be induced by physically or mentally demanding situations. Moreover, even in the absence of extreme conditions, tyrosine may improve convergent thinking. Nevertheless, our review did not yield convincing evidence that tyrosine can acutely improve endurance exercise performance.

The mixed results on endurance exercise performance suggest that tyrosine loading may not be very useful in this context: only one out of six similarly designed studies found tyrosine to enhance performance relative to placebo (Tumilty et al., 2011). This suggests that tyrosine loading may not be sufficient to counteract exercise-induced physical fatigue. Athletes interested in augmenting endurance exercise performance should not expect significant performance increases from taking tyrosine before a work-out.

For athletes whose sport requires fine motor skills and a lot of cognitive effort to perform well, tyrosine has greater potential as an effective performance aid. For example, in one study tyrosine was able to acutely protect cold-induced decrements in marksmanship accuracy (O'Brien et al., 2007). Moreover, tyrosine loading had consistent effects on working memory and information processing, which suggests that tyrosine could help athletes in sports that demand cognitive and psychomotor performance under difficult conditions, such as biathlon.

Tyrosine could aid performance not only in sports, but also in occupational contexts. When a situation imposes heavy cognitive loads or harsh environmental conditions upon people, tyrosine is able to prevent or reverse the cognitive performance decrements induced by these conditions. Tyrosine could thus aid workers in demanding office jobs or military soldiers on a mission. As tyrosine can improve convergent thinking (Colzato et al., 2014), in academia tyrosine might help students improve their focus while studying. This suggests that tyrosine might provide an alternative to frequently used "study drugs" such as methylphenidate (Babcock and Byrne, 2000). The effects of tyrosine loading on working memory and information processing speed appear to be similar to those of methylphenidate (Linssen et al., 2014). At the same time, the side effects of tyrosine appear to be milder and less frequent (Young, 1996) than those of methylphenidate (Linssen et al., 2014), though toxicity data on their long-term use are lacking.

In the only study to use a longitudinal design, tyrosine or placebo was supplemented for two seasons to research station residents in Antarctica (Palinkas et al., 2007). While mood improved in the tyrosine group and worsened in the placebo group over the course of the winter, in the summer the tyrosine group did not differ from the placebo group in terms of mood. Even the Antarctic summer is very cold, with a January high of −2.9 °C. This brings about the question of why tyrosine's effects on mood were different in the two seasons. One possible explanation lies in the total absence of sunlight for several weeks during the winter. As previous research has shown that the detrimental effects of experimental tyrosine depletion on mood are larger in dim light than in bright light (Cawley et al., 2013), one could hypothesize that tyrosine supplementation can exert a larger effect on mood in the absence of sunlight than in its presence, i.e. during the summer. In line with this hypothesis, animal studies suggest that short days increase dopamine turnover in the pituitary (Steger et al., 1995) and suppress tyrosine hydroxylase expression in the prefrontal cortex (Sorg et al., 2011). This can help explain why tyrosine is more likely to influence mood during the winter than during the summer.

Indirect support for the mitigation of performance decrements by tyrosine was obtained by looking at biomarkers of brain functioning (Kishore et al., 2013; Palinkas et al., 2007). For example, tyrosine prevented heat-induced increases in P300 latency assessed using an auditory odd-ball paradigm (Kishore et al., 2013). This suggests that tyrosine might counteract information processing decrements under stressful circumstances. This idea is consistent with research linking the P300 response with alterations in the firing of norepinephrine neurons in the *locus coeruleus* (Nieuwenhuis et al., 2005). As stated in the Introduction, the catecholamine depletion hypothesis proposes that tyrosine can exert beneficial effects when brain catecholamine levels are low and there is more room for tyrosine to be converted into L-DOPA, which then gets converted into dopamine and norepinephrine (Fernstrom and Fernstrom, 2007; O'Brien et al., 2007; Colzato et al.,

2013). Hence, alterations in *locus coeruleus* firing could be mitigated by the increases in norepinephrine synthesis caused by tyrosine loading (Devilbiss and Berridge, 2006; Bari and Aston-Jones, 2013), thus restoring the *Locus coeruleus* signal that is represented in the P300 response.

Some results posed new questions. In the Antarctica study (Palinkas et al., 2007), plasma norepinephrine levels declined less in the tyrosine group than in the placebo group over the course of the Antarctic summer. This is consistent with the catecholamine depletion hypothesis in that tyrosine, as a norepinephrine precursor, should be able to buffer a decline in norepinephrine. However, this pattern was reversed in the Antarctic winter, when plasma norepinephrine levels declined more in the tyrosine group. If plasma norepinephrine levels are a biomarker of brain norepinephrine levels, then this latter finding is inconsistent with the catecholamine depletion hypothesis. We have no good explanation for the finding, though it is possible that in the total absence of sunlight for several weeks during the winter, tyrosine hydroxylase activity was so low that all of the tyrosine available in blood plasma would quickly be taken up by the brain and converted into L-DOPA, resulting in plasma norepinephrine levels no longer reflecting brain norepinephrine levels.

One study found that tyrosine loading resulted in an increase in plasma prolactin levels during physical exercise (Strüder et al., 1998). This was unexpected because the release of prolactin from the anterior pituitary is inhibited, rather than stimulated, by dopamine in the brain (Strüder et al., 1998; Harmer et al., 2001). Given that tyrosine loading would be expected to increase brain dopamine levels, a subsequent decrease in plasma prolactin levels would have been expected. Again, we cannot readily explain this finding, though it is possible that the administered tyrosine was transported to the skeletal muscles rather than to the brain. During exercise, blood flow to the skeletal muscles increases (Andersen and Saltin, 1985), presumably resulting in less blood flow to the brain. This idea, though controversial, could explain why exercise performance did not acutely increase after tyrosine loading (assuming that exercise performance is under the control of brain dopamine).

The studies included in this systematic review used randomized double-blind, placebo-controlled designs (see Table 1). This suggests that their quality was better than that of the case studies and mostly uncontrolled studies previously described by Young (1996). However, there are boundaries to their implications, due to some limitations. For instance, the total number of selected studies was limited. Further, as their sample sizes were small to moderate, the absence of significant effects of tyrosine on endurance exercise performance in particular should be interpreted with caution. Furthermore, some studies used a placebo that was rich in carbohydrates (e.g., orange juice), which may have inadvertently affected brain uptake of tyrosine (Wurtman et al., 2003). Finally, only one study used daily tyrosine supplementation over the course of multiple weeks rather than acute loading on a single test day. More research is required to substantiate the findings of the supplementation study. Nevertheless, one additional longitudinal study not included in our review due to its case study design without a control condition found that tyrosine supplementation, ranging from a few months to several years, was able to improve strength and motor control in children and adolescents with nemaline myopathy (Ryan et al., 2008). This suggests that even though tyrosine may not have any acute effects (Strüder et al., 1998; Sutton et al., 2005; Chinevere et al., 2002; Tumilty et al., 2014; Watson et al., 2012), it might enhance endurance exercise performance over longer time periods.

Given the promising findings of tyrosine loading studies on cognition (O'Brien et al., 2007; Colzato et al., 2013, in press; Mahoney et al., 2007; Kishore et al., 2013; Thomas et al., 1999) and the paucity of tyrosine supplementation studies to date, we propose that future research should focus on administering tyrosine over longer periods of time. Given the observed effect sizes in acute loading studies, it seems worth investigating whether tyrosine can bring the same benefits in studies employing tyrosine supplementation. If positive effects were also observed over longer time periods, then this could enable organizations to improve employee performance in jobs that expose workers to frequent physical or mental stressors, such as extreme temperatures or high cognitive demands at work. Also, longitudinal studies could test the potential role of tyrosine in alleviating negative reactions to a lack of sunlight (Cawley et al., 2013). This might be particularly relevant to individuals diagnosed with seasonal affective disorder, who show a marked worsening of mood in the winter, presumably as a result of the shortening of days in the fall and the associated changes in the brain dopamine system (Depue et al., 1989).

5. Conclusions

We conclude that increased tyrosine intake can have beneficial effects on psychological functioning. Behavioral effects have not been consistently supported, but low sample sizes limit the conclusions of the respective studies. Though the effectiveness of loading and supplementation may differ across circumstances and applications, tyrosine can exert notable acute cognitive benefits when the situation demands for an increased availability of the catecholamines, and may also benefit some individuals emotionally when administered over longer time periods.

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