RETRACTED CHAPTER: Tyrosine

Lorenza S. Colzato

Introduction

The amino acid L-tyrosine (TYR) is the chemical forerunner of dopamine (DA). Under specific circumstances, TYR administration can augment DA levels in the brain (Cuche et al. 1985; Gibson and Wurtman 1977; Tam et al. 1990) and because of that several studies have investigated whether the supplementation of TYR can have a beneficial effect on cognitive and behavioral performance that depends on DA function. However, outcomes on the effectiveness of TYR supplementation are mixed: some studies show positive effects, whereas others do not. The present chapter, adapted from Jongkees et al. (2015), reviews the available TYR studies to elucidate under which conditions TYR has a beneficial effect on cognitive performance. The focus will be on healthy humans and not on clinical populations associated with suboptimal catecholamine levels.

First, I will describe how TYR supplementation impacts DA function, given that the nature of this mechanism may play a pivotal role in determining whether and to what extent supplementation can promote performance. Second, I will outline the available studies on stress, which decreases DA levels in the brain via increased turnover rates and leads to associated impairments in performance (Lehnert et al. 1984; Mahoney et al. 2007). Accordingly, TYR administration has been suggested as a potential counter-actor of stress-induced decline in performance. Third, I will review studies on healthy humans in cognitively demanding situations, which

The original version of this chapter was retracted: The retraction note to this chapter is available at https://doi.org/10.1007/978-3-319-57505-6_24

L.S. Colzato (✉)
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

L.S. Colzato
Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
https://doi.org/10.1007/978-3-319-57505-6_1

create a stress-like state that might lead to DA depletion and associated cognitive decline that might be reversed by TYR administration. The outcomes of the reviewed studies point out that TYR supplementation has the potential to promote cognitive performance, particularly in short-term stressful and/or cognitively demanding situations and when individual differences related to DA baseline levels are taken into account.

Mechanism of Action

Plasma TYR levels peak between 1 and 2 h after ingestion and can stay significantly elevated up to 8 h (Glaeser et al. 1979). Accordingly, in rats it has been found that prefrontal DA was raised 1 h after TYR intake, but not earlier (Tam et al. 1990). Once it has passed the blood–brain barrier and is taken up by the appropriate brain cells, the enzyme tyrosine-hydroxylase (Daubner et al. 2011) converts TYR into L-DOPA. At first tyrosine-hydroxylase activity increases upon consumption of TYR, but its activity is downregulated by end-product inhibition (Daubner et al. 2011; Tam et al. 1990), which prevents large increases in DA release. In a second step, L-DOPA is converted into DA leading to an elevation in DA level, see Fig. 1.

Notably, TYR has been shown to enhance neurotransmitter synthesis only in actively firing neurons (Fernstrom and Fernstrom 2007; Lehnert et al. 1984; Tam et al. 1990). This points to the fact that TYR can counteract neurotransmitter depletion, a process in which enhanced brain activity induces decrements in DA levels and associated behavioral performance decline. Indeed, when subjected to stress or a cognitively challenging task, DA neurons become more active and their synthesis rate raises (Kvetnansky et al. 2009; Lehnert et al. 1984; Mahoney et al. 2007). As a result, more DA is synthesized from TYR in order to meet the situational demands. However, the conversion of TYR into DA becomes limited when TYR levels decline. This process is responsible for less DA availability and resulting declines in performance (Goldman-Rakic et al. 2000; Muly et al. 1998). In this situation, brain function might benefit from TYR administration, which allows DA synthesis to carry on and maintain DA levels necessary to guarantee optimal performance (Wurtman et al. 1981). This role of TYR as a *depletion counter-actor* seems to take place only in actively firing neurons. Indeed, in rats it has been demonstrated that TYR supplementation only increased DA synthesis in the striatum when this region was pharmacologically activated (Tam et al. 1990). That is, TYR administration seems to have a positive effect only in circumstances that encourage neurotransmitter synthesis, i.e., circumstances that are sufficiently stressful or challenging. Accordingly, this chapter will show that TYR's role as a *depletion counter-actor* corresponds to the outcomes found in the literature.

The World Health Organization's daily upper requirement of TYR is 14 mg/kg (see Deijen 2005), suggesting that an individual weighing 70 kg should consume daily about 1 g of TYR for normal functioning. It is questionable whether doses above 1 g are likely to add any further benefits, given that the rate-limiting tyrosine-hydroxylase enzyme is supposed to be close to saturation in normal

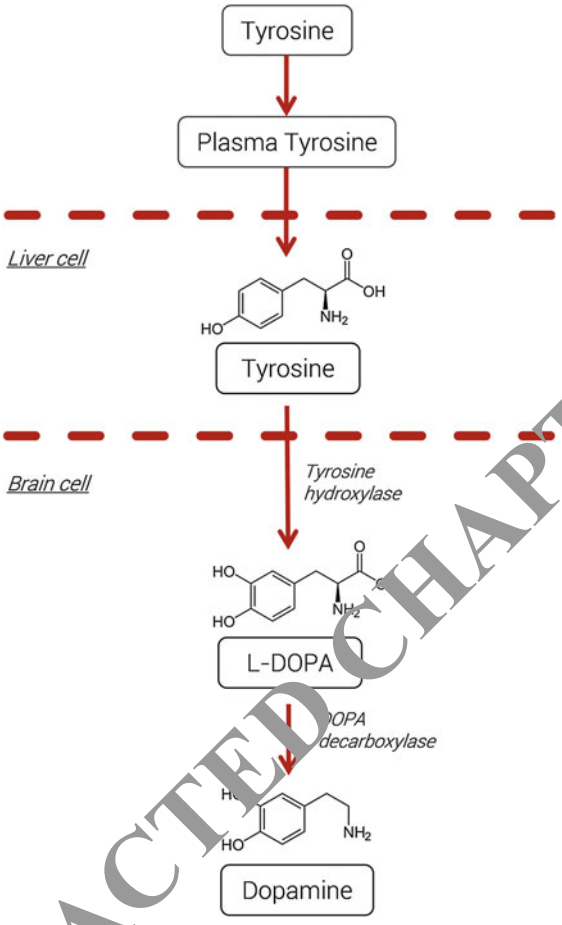

Fig. 1 Schematic representation of the effect of acute tyrosine supplementation on tyrosine to dopamine conversion. Once it has passed the blood–brain barrier the enzyme tyrosine-hydroxylase converts tyrosine into L-DOPA. In a second step, L-DOPA is converted, via the enzyme DOPA decarboxylase, into dopamine leading to an elevation in dopamine level

competition (Brodnik et al. 2012). Indeed, TYR transport across cell membranes is reduced in healthy humans after TYR administration (Wiesel et al. 1999). That is, extra TYR would thus be metabolized rather than converted into L-DOPA. While too much TYR might not contribute to additional benefits, consuming too little might also not be beneficial. Moreover, TYR shares a transporter across the blood–brain barrier with several other large neutral amino acids such as phenylalanine and tryptophan (Fernstrom 1990). Accordingly, the amount of TYR that crosses the blood–brain barrier instead of being metabolized peripherally relies on the individual's levels of these other amino acids. Studies exploring the effect of acute TYR administration should thus have their subjects fast overnight to limit competition

from other amino acids. However, in long-term studies this is not advisable given that completely avoiding these other amino acids for longer periods might not be feasible nor recommendable.

One may argue that L-DOPA might be preferable to TYR because it circumvents issues such as the competition from other amino acids and the rate-limiting tyrosine-hydroxylase. Nonetheless, there are a number of factors why TYR supplementation might be more suitable. On the one hand, the fact that the tyrosine-hydroxylase enzyme is already close to saturation under normal circumstances has the advantage to prevent large quantities of TYR be converted. In contrast, the conversion of L-DOPA into DA does not rely on a similar rate-limiting factor, which significantly increases the possibility of leading to "overdose" DA levels that are harmful for performance (Goldman-Rakic et al. 2000; Muly et al. 1998). Taking into account the inverted-U profile of DA (Cools and D'Esposito 2011), it is likely for L-DOPA supplementation to boost individuals to the lower right end of the curve, while the subtle increment from TYR is unlikely to lead to any "overdose" effect. There are currently no established side-effects of long-term TYR administration, even though one study found more saccadic intrusions during smooth-pursuit eye movement performance in patients with schizophrenia (Deutsch et al. 1994). On the other hand, chronic L-DOPA supplementation has been linked to adverse side-effects such as insomnia, dyskinesia, nausea, and in some cases even psychosis (Foster and Hoffer 2004; Leggins et al. 2012). It should be acknowledged that studies on the chronic effect of TYR administration are still limited and its potential long-term side-effects should be more extensively explored before inferring final conclusions. Notably, even though the beneficial effects of TYR during long-term stress are less investigated, the outcomes are encouraging. It has been shown that prolonged stress exposure (e.g., low temperatures) can enhance TH activity up to one month, suggesting TYR might be especially useful during winter. After one month, however, tyrosine-hydroxylase activity is no longer significantly elevated (Kvetnansky et al. 2009). Nonetheless, DA neurons stay highly active, leading to a depletion of DA levels (Kvetnansky et al. 2009). This result indicates that TYR can also have positive effects in long-term situations. Along the same line, a study in Antarctica residents (Palinkas et al. 2007) found TYR to exhibit beneficial effects even after 7 weeks of exposure to extreme cold.

Enhancing Cognitive Performance in Stressful Conditions

Stress causes enhanced DA activity and turnover rates in the brain, inducing the depletion of DA levels as well as behavioral depression (Kvetnansky et al. 2009; Lehnert et al. 1984). Nonetheless, studies that supplemented TYR to rats before stress exposure have shown that DA depletion and declines in performance can be compensated (Lehnert et al. 1984; Lieberman et al. 2005; Rauch and Lieberman 1990; Shurtleff et al. 1993; Yeghiayan et al. 2001). These outcomes inspired several studies exploring whether and under which circumstances TYR can also promote

human performance during stress. These studies often targeted either physical exercise or cognitive functions.

Studies on TYR and physical exercise have primarily targeted endurance exercise, postulating that sustaining adequate DA levels in the brain can maintain the incentive to optimize performance. Two studies have explored TYR and endurance exercise without an additional overt stressor, but neither found any enhancement after TYR supplementation (Chinevere et al. 2002; Sutton et al. 2005). Other studies have examined exercise performance during heat exposure, but the outcomes were inconsistent. One study showed TYR induces longer exercise times in the absence of an increase in ratings of perceived effort and thermal sensation (Tumilty et al. 2011), indicating that TYR did indeed enhance endurance. Nonetheless, these outcomes were not replicated in two later studies (Tumilty et al. 2014; Watson et al. 2012). Hence, there is no reliable evidence TYR promotes physical exercise performance, e.g., endurance, in stressful circumstances. This suggests that physical performance *can* be promoted by TYR administration, but only under specific circumstances that activate DA neurons and mobilize higher cognitive functions such as attention and cognitive control. That is, TYR administration seems to enhance physical performance only when it recruits individual high enough cognitive demands that lead to DA depletion. Accordingly, studies exhibiting no effect of TYR might then have investigated exercise that did not sufficiently recruit cognitive processes. This hypothesis is supported by several outcomes showing that TYR is effective at promoting cognition during stress, as discussed below.

It is noteworthy, in contrast to the above-mentioned studies, TYR reliably has a beneficial effect on cognitive performance when healthy humans ingest TYR before stress exposure. In such studies, hypothermia is often used as a stressor and TYR has been consistently shown to counteract the decrements in cognition it may cause (Mahoney et al. 2007; O'Brien et al. 2007; Shurtleff et al. 1994). These studies explored working memory, a key cognitive function that entails actively maintaining and updating information in memory (Baddeley and Hitch 1974; Miyake et al. 2000). Given that working memory is modulated by DA (Cools et al. 2008; Goldman-Rakic et al. 2000; Moustafa et al. 2008; Siessmeier et al. 2006), this function has been often investigated in relation to TYR. In particular, changes in DA levels due to TYR are expected to modulate working memory performance. All studies described cold exposure to reduce working memory performance; however, this decline was counteracted when the participants were administered TYR. Banderet and Lieberman (1989) investigated TYR and exposure to cold in relation to a broad range of cognitive functions. The authors described benefits in vigilance and reaction times on several tasks. Interestingly, they restricted their analysis to "those individuals most affected by exposure to the cold" (p. 760), indicating TYR only enhances individuals who would otherwise have been stressed by the coldness. This possibility highlights the utility of taking into account individual differences when examining the effects of TYR (Jongkees et al. 2014). Along the same lines, performance on the Stroop task and working memory has been promoted by TYR administration while participants were exposed to an auditory stressor (Deijen and Orbleke 1994). Similarly, performance on working memory, reasoning, and vigilance has been enhanced by TYR during sleep deprivation (Magill et al. 2003).

Moreover, TYR has also been found to enhance both cognitive and behavioral performance in army cadets after an intensive combat training course. Nonetheless, it is hard to draw conclusions from this study, given that many other amino acids were administered jointly with TYR and the placebo-group did not receive a completely neutral placebo (Deijen et al. 1999).

Finally, some studies have explored whether TYR can counteract stress-induced mood declines. Palinkas et al. (2007) administered TYR to residents of Antarctica, with the goal to enhance mood during protracted cold climate exposure. The hostile environment of Antarctica can be regarded a multi-stressor intervention including confinement and isolation as well as the inherent cold. Notably, Palinkas and colleagues showed that TYR improved mood, but only during the winter. This study is one of few that investigates TYR administration in healthy individuals in a long-term situation. The outcome is in line with the result by Banderet and Lieberman (1989) that TYR counteracted cold-induced decrements in mood. On the contrary, TYR did not to enhance mood without stress exposure (Leathwood and Pollet 1983; Lieberman et al. 1983). These outcomes indicate TYR might have a positive effect on mood, but only in stressful situations such as extreme cold.

In sum, the beneficial effects of TYR on cognitive performance are likely due to TYR counteracting a decline of DA availability during stress (Banderet and Lieberman 1989; Kvetnansky et al. 2009; Lehnert et al. 1984), which precludes declines in higher cognitive functions such as attention and working memory. For instance, TYR's enhancing effect on working memory and attention, found in many studies, might be due to TYR supporting an optimal level of DA necessary for a balance between stable cognitive representations versus flexible updating of those representations (Cools and D'Esposito 2011).

Enhancing Cognitive Demands in Healthy Humans

This section reviews studies on TYR administration in healthy humans who were not explicitly and directly exposed to stressors that may affect their performance. Rather, these studies included challenging cognitive tasks that were assumed to be demanding enough to lead to a stress-like state that causes DA depletion and decreased levels of performance, an effect TYR may reverse.

In line with the above-mentioned studies on stress, so far, two studies have found that TYR can promote working memory performance, but in the absence of a direct exposure to stress. Rather, beneficial effects were only found under particularly demanding circumstances. In particular, Thomas et al. (1999) found TYR only enhanced working memory when other tasks were performed at the same time. Moreover, TYR has been found to enhance working memory even in a single-task setting, but only in the task's more challenging condition that places a higher load on memory (Colzato et al. 2013). The outcomes of these two studies support the idea that TYR can enhance cognitive performance and emphasize the crucial role of TYR as counter-actor in performance-degrading conditions.

In addition to working memory, Colzato et al. (2014) have found TYR to selectively enhance the ability to stop on time (an index of inhibitory control) without affecting response execution. Moreover, a new study has found that TYR can enhance cognitive flexibility as indexed by a task-switching paradigm: TYR likely promoted performance by supporting conflict-resolving processes that may have in other circumstances produced a stressful state (Steenbergen et al. 2015). Furthermore, TYR has also been found to enhance performance on a convergent-thinking task (Colzato et al. 2015). All three above-mentioned studies are particularly relevant because the cognitive functions investigated are assumed to depend on DA-driven cognitive control (Cools and D'Esposito 2011). Hence, these outcomes point to the possibility that positive effects induced by TYR may be mediated by increased DA function. None of the studies describes an effect of TYR on mood, but this was expected given that mood was not reduced even in the placebo conditions, so there was no decline to reverse.

Finally, a recent study for the first time took into account individual differences (i.e., genetic differences) in base levels of DA to explain the effectivity of TYR. Indeed, it is likely that depending on this DA baseline levels, some people may benefit more than others from TYR intake (Jongkees et al. 2014). The study showed evidence supporting the idea that TYR supplementation may function as a cognitive enhancer and compensate for unfavorable genetic predisposition. TYR was administered to participants, genotyped for the C957T polymorphism at the DRD2 gene (polymorphism related to the striatal DA level). Measures of working memory updating and inhibitory control were acquired. T/T homozygotes (i.e., individuals associated with lower striatal DA level) showed larger beneficial effects of TYR supplementation than C/C homozygotes (i.e., individuals associated with higher striatal DA level). These findings reinforce the idea that genetic predisposition modulates the effect of TYR in its role as cognitive enhancer (Jongkees et al. 2014; Colzato et al. 2016).

In sum, the outcomes described in this section suggest TYR can improve cognitive performance without direct exposure to stress, but only if performance would normally be impaired by high cognitive demands. Indeed, high cognitive challenges lead to a stress-like state inducing DA depletion and associated cognitive impairments, which are then reversed by TYR. Moreover, the effectivity of TYR seems to depend on individual DA baseline levels.

Conclusion

TYR, the chemical forerunner of DA, has the promising potential to increase DA function in the brain in challenging situations. The mechanisms of action of TYR are to help the brain to maintain an elevated rate of DA synthesis when the brain needs it the most.

The potential of TYR for enhancing physical exercise during stress seems restricted; probably because physical performance is not as straight related to DA levels in the brain as cognitive performance is. Accordingly, this suggests physical

exercise may profit from TYR only to the degree that it recruits a stressful state in which cognitive control functions are required and DA levels are reduced.

TYR seems to show the most reliable beneficial effects on cognitive performance when healthy humans are exposed to either external stressors or cognitively challenging circumstances. Under these conditions, DA levels in the brain decrease and, consequently, performance on cognitive tasks declines. TYR supplementation acts as a cognitive enhancer by refilling DA levels in the brain and compensate for the stress-induced impairment of a variety of cognitive functions. This improvement is modulated by DA baseline levels (i.e., genetic differences) and is due to an increase of DA function in striatal or prefrontal areas, which is closely associated with cognitive control functions, such as cognitive flexibility, working memory updating, and response inhibition.

In nutshell, TYR seems to be a very promising cognitive enhancer but only when individuals find themselves in stressful or cognitively demanding situations and, in particular, when individual differences are taken into account.

References

Baddeley, A. D., & Hitch, G. (1974). Working memory. In G. H. Bower (Ed.), *The psychology of learning and motivation: Advances in research and theory* (pp. 47–89). New York: Academic Press.

Banderet, L. E., & Lieberman, H. R. (1989). Treatment with tyrosine, a neurotransmitter precursor, reduces environmental-stress in humans. *Brain Research Bullettin, 22,* 759–762.

Brodnik, Z., Bongiovanni, R., Double, M., & Jaskiw, G. E. (2012). Increased tyrosine availability increases brain regional DOPA levels in vivo. *Neurochemestry International, 61,* 1001–1006.

Chinevere, T. D., Sawyer, R. D., Cretzmeyer, A. R., Conlee, R. K., & Parcell, A. C. (2002). Effects of L-tyrosine and carbohydrate ingestion on endurance exercise performance. *Journal of Applied Physiology, 93,* 1590–1597.

Colzato, L. S., De Haan, A., & Hommel, B. (2015). Food for creativity: Tyrosine promotes performance in a convergent-thinking task. *Psychological Research, 79,* 709–714.

Colzato, L. S., Jongkees, B., Sellaro, R., & Hommel, B. (2013). Working memory reloaded: Tyrosine replenishes updating in the N-Back task. *Frontiers in Behavioral Neuroscience, 7,* 200.

Colzato, L. S., Jongkees, B. J., Sellaro, R., van den Wildenberg, W., & Hommel, B. (2014). Eating to stop: Tyrosine supplementation enhances inhibitory control but not response execution. *Neuropsychologia, 62,* 398–402.

Colzato, L. S., Steenbergen, L., Sellaro, R., Stock, A. K., Arning, L., & Beste, C. (2016). Effects of L-Tyrosine on working memory and inhibitory control are determined by DRD2 genotypes: A randomized controlled trial. *Cortex, 82,* 217–224.

Cools, R., & D'Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biological Psychiatry, 69,* 113–125.

Cools, R., Gibbs, S. E., Miyakawa, A., Jagust, W., & D'Esposito, M. (2008). Working memory capacity predicts dopamine synthesis capacity in the human striatum. *Journal of Neuroscience, 28,* 1208–1212.

Cuche, J. L., Prinseau, J., Selz, F., Ruget, G., Tual, J. L., Reingeissen, L., et al. (1985). Oral load of tyrosine or L-DOPA and plasma levels of free and sulfoconjugated catecholamines in healthy men. *Hypertension, 7,* 81–89.

Daubner, S. C., Le, T., & Wang, S. Z. (2011). Tyrosine hydroxylase and regulation of dopamine synthesis. *Archives of Biochemistry and Biophysics, 508,* 1–12.

Deijen, J. B. (2005). Tyrosine. In H. R. Lieberman, R. B. Kanarek, & J. F. Orbleke (Eds.), *Nutrition Brain and Behavior* (pp. 363–381). Boca Raton: CRC Press.

Deijen, J. B., & Orlebeke, J. F. (1994). Effect of tyrosine on cognitive function and blood pressure under stress. *Brain Research Bulletin, 33,* 319–323.

Deijen, J. B., Wientjes, C. J. E., Vullinghs, H. F. M., Cloin, P. A., & Langefeld, J. J. (1999). Tyrosine improves cognitive performance and reduces blood pressure in cadets after one week of a combat training course. *Brain Research Bulletin, 48,* 203–209.

Deutsch, S. I., Rosse, R. B., Schwartz, B. L., Banay-Schwartz, M., McCarthy, M. F., & Johri, S. K. (1994). L-tyrosine pharmacotherapy of schizophrenia: Preliminary data. *Clinical Neuropharmacology, 17,* 53–62.

Fernstrom, J. D. (1990). Aromatic amino acids and monoamine synthesis in the central nervous system: Influence of the diet. *Journal of Nutritional Biochemistry, 1,* 508–517.

Fernstrom, J. D., & Fernstrom, M. H. (2007). Tyrosine, phenylalanine, and catecholamine synthesis and function in the brain. *Journal of Nutrition, 137,* 1539S–1547S.

Foster, H. D., & Hoffer, A. (2004). The two faces of L-DOPA: Benefits and adverse side effects in the treatment of encephalitis lethargica, Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis. *Medical Hypotheses, 62,* 177–181.

Gibson, C. J., & Wurtman, R. J. (1977). Physiological control of brain catechol synthesis by brain tyrosine concentration. *Biochemical Pharmacology, 26,* 1137–1142.

Glaeser, B. S., Melamed, E., Growdon, J. H., & Wurtman, R. J. (1979). Elevation of plasma tyrosine after a single oral dose of L-tyrosine. *Life Sciences, 25,* 265–271.

Goldman-Rakic, P. S., Muly, E. C., & Williams, G. V. (2000). D1 receptors in prefrontal cells and circuits. *Brain Research Review, 31,* 295–301.

Jongkees, B. J., Hommel, B., & Colzato, L. S. (2014). People are different: Tyrosine's modulating effect on cognitive control may depend on individual differences related to dopamine function. *Frontiers in Psychology, 5,* 1101.

Jongkees, B. J., Hommel, B., Kühn, S., & Colzato, L. S. (2015). Effect of tyrosine supplementation on clinical populations and healthy populations under stress or cognitive demands: A review. *Journal of Psychiatric Research, 70,* 50–57.

Kvetnansky, R., Sabban, E. L., & Palkovits, M. (2009). Catecholaminergic systems in stress: Structural and molecular genetic approaches. *Physiological Reviews, 89,* 535–606.

Leathwood, P. D., & Pollet, P. (1983). Diet-induced mood changes in normal-populations. *Journal of Psychiatry Research, 17,* 147–154.

Lehnert, H., Reinstein, D. K., Strowbridge, B. W., & Wurtman, R. J. (1984). Neurochemical and behavioral consequences of acute uncontrollable stress: Effects of dietary tyrosine. *Brain Research, 303,* 215–223.

Lieberman, H. R., Corkin, S., Spring, B. J., Growdon, J. H., & Wurtman, R. J. (1983). Mood, performance, and pain sensitivity: Changes induced by food constituents. *Journal of Psychiatry Research, 17,* 135–145.

Lieberman, H. R., Georgelis, J. H., Maher, T. J., & Yeghiayan, S. K. (2005). Tyrosine prevents effects of hyperthermia on behavior and increases norepinephrine. *Physiology & Behavior, 84,* 23–30.

Riggins, J., Pihl, R. O., Benkelfat, C., & Leyton, M. (2012). The dopamine augmenter L-DOPA does not affect positive mood in healthy human volunteers. *PLoS ONE, 7,* e28370.

Magill, R. A., Waters, W. F., Bray, G. A., Volaufova, J., Smith, S. R., Lieberman, H. R., et al. (2003). Effects of tyrosine, phentermine, caffeine D-amphetamine, and placebo on cognitive and motor performance deficits during sleep deprivation. *Nutritional Neuroscience, 6,* 237–246.

Mahoney, C. R., Castellani, J., Kramer, F. M., Young, A., & Lieberman, H. R. (2007). Tyrosine supplementation mitigates memory decrements during cold exposure. *Physiology & Behavior, 92,* 575–582.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive Psychology, 41,* 49–100.

Moustafa, A. A., Sherman, S. J., & Frank, M. J. (2008). A dopaminergic basis for working memory, learning and attentional shifting in Parkinsonism. *Neuropsychologia, 46,* 3144–3156.

Muly, E. C., III, Szigeti, K., & Goldman-Rakic, P. S. (1998). D1 receptor in interneurons of macaque prefrontal cortex: Distribution and subcellular localization. *Journal of Neuroscience, 18,* 10553–10565.

O'Brien, C., Mahoney, C., Tharion, W. J., Sils, I. V., & Castellani, J. W. (2007). Dietary tyrosine benefits cognitive and psychomotor performance during body cooling. *Physiology & Behavior, 90,* 301–307.

Palinkas, L. A., Reedy, K. R., Smith, M., Anghel, M., Steel, G. D., Reeves, D., et al. (2007). Psychoneuroendocrine effects of combined thyroxine and triiodothyronine versus tyrosine during prolonged antarctic residence. *International Journal of Circumpolar Health, 66,* 401–417.

Rauch, T. M., & Lieberman, H. R. (1990). Tyrosine pretreatment reverses hypothermia-induced behavioral depression. *Brain Research Bulletin, 24,* 147–150.

Shurtleff, D., Thomas, J. R., Ahlers, S. T., & Schrot, J. (1993). Tyrosine ameliorates a cold-induced delayed matching-to-sample performance decrement in rats. *Psychopharmacology (Berl), 112,* 228–232.

Shurtleff, D., Thomas, J. R., Schrot, J., Kowalski, K., & Harford, R. (1994). Tyrosine reverses a cold-induced working-memory deficit in humans. *Pharmacology, Biochemistry and Behavior, 47,* 935–941.

Siessmeier, T., Kienast, T., Wrase, J., Larsen, J. L., Braus, D. F., Smolka, M. N., et al. (2006). Net influx of plasma 6-[F-18]fluoro-L-DOPA (FDOPA) to the ventral striatum correlates with prefrontal processing of affective stimuli. *European Journal of Neuroscience, 24,* 305–313.

Steenbergen, L., Sellaro, R., Hommel, B., & Colzato, L. S. (2015). Tyrosine promotes cognitive flexibility: Evidence from proactive vs. reactive control during task switching performance. *Neuropsychologia, 69,* 50–55.

Sutton, E. E., Coill, M. R., & Deuster, P. A. (2005). Ingestion of tyrosine: Effects on endurance, muscle strength, and anaerobic performance. *International Journal of Sport Nutrition and Exercise Metabolism, 15,* 173–185.

Tam, S. Y., Elsworth, J. D., Bradberry, C. W., & Roth, R. H. (1990). Mesocortical dopamine neurons: High basal firing frequency predicts tyrosine dependence of dopamine synthesis. *Journal of Neural Transmission, 81,* 97–110.

Thomas, J. R., Lockwood, P. A., Sing, A., & Deuster, P. A. (1999). Tyrosine improves working memory in a multitasking environment. *Pharmacology, Biochemistry and Behavior, 64,* 495–500.

Tumilty, L., Davison, G., Beckmann, M., & Thatcher, R. (2011). Oral tyrosine supplementation improves exercise capacity in the heat. *European Journal of Applied Physiology, 111,* 2941–2950.

Tumilty, L., Davison, G., Beckmann, M., & Thatcher, R. (2014). Failure of oral tyrosine supplementation to improve exercise performance in the heat. *Medicine & Science in Sports Exercise, 46,* 1417–1425.

Watson, P., Enever, S., Page, A., Stockwell, J., & Maughan, R. J. (2012). Tyrosine supplementation does not influence the capacity to perform prolonged exercise in a warm environment. *International Journal of Sport Nutrition and Exercise Metabolism, 22,* 363–373.

Wiesel, F. A., Andersson, J. L. R., Westerberg, G., Wieselgren, I. M., Bjerkenstedt, L., Hagenfeldt, L., et al. (1999). Tyrosine transport is regulated differently in patients with schizophrenia. *Schizophrenia Research, 40,* 37–42.

Wurtman, R. J., Hefti, F., & Melamed, E. (1981). Precursor control of neurotransmitter synthesis. *Pharmacological Reviews, 32,* 315–335.

Yeghiayan, S. K., Luo, S. Q., Shukitt-Hale, B., & Lieberman, H. R. (2001). Tyrosine improves behavioral and neurochemical deficits caused by cold exposure. *Physiology & Behavior, 72,* 311–316.