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Review

Effect of tyrosine supplementation on clinical and healthy populations under stress or cognitive demands—A review

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ABSTRACT

Consuming the amino-acid tyrosine (TYR), the precursor of dopamine (DA) and norepinephrine (NE), may counteract decrements in neurotransmitter function and cognitive performance. However, reports on the effectiveness of TYR supplementation vary considerably, with some studies finding beneficial effects, whereas others do not. Here we review the available cognitive/behavioral studies on TYR, to elucidate whether and when TYR supplementation can be beneficial for performance. The potential of using TYR supplementation to treat clinical disorders seems limited and its benefits are likely determined by the presence and extent of impaired neurotransmitter function and synthesis. Likewise, the potential of TYR supplementation for enhancing physical exercise seems minimal as well, perhaps because the link between physical exercise and catecholamine function is mediated by many other factors. In contrast, TYR does seem to effectively enhance cognitive performance, particularly in short-term stressful and/or cognitively demanding situations. We conclude that TYR is an effective enhancer of cognition, but only when neurotransmitter function is intact and DA and/or NE is temporarily depleted.

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1. Introduction

The amino-acid L-Tyrosine (TYR) is the biochemical precursor of the catecholamines dopamine (DA) and norepinephrine (NE). Given the right circumstances TYR supplementation can enhance DA and NE levels in the brain (Cuche et al., 1985; Gibson and Wurtman, 1977; Tam et al., 1990) and this possibility has led numerous studies to investigate whether administration of TYR can positively influence cognitive or behavioral performance that relies on catecholamine function. Unfortunately, reports on the effectiveness of TYR supplementation have varied greatly, with some studies showing a marked positive effect, whereas others report no

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significant changes. Here we provide a summary review of the available cognitive and behavioral TYR studies and their main results, to gain a better understanding of the conditions under which TYR has a positive effect and whether TYR may be useful in a clinical context. Further, we hope to help inform future studies on how to best design and analyze experiments regarding TYR.

Before we review the behavioral and cognitive studies on TYR, we will first elaborate on the mechanism through which TYR presumably enhances brain physiology. As we will argue, the nature of this mechanism might play a crucial role in determining whether and to what extent supplementation can benefit performance. Plasma TYR levels peak between 1 and 2 h after consumption and can remain significantly elevated up to 8 h (Glaeser et al., 1979). Correspondingly, in rats it was shown prefrontal DA increased 1 h after TYR administration, but not earlier (Tam et al., 1990). Once it has passed the blood–brain barrier (BBB) and is taken up by the appropriate brain cells, TYR is converted into L-DOPA through an enzyme called tyrosine-hydroxylase (TH; Daubner et al., 2011). TH activity initially increases upon consumption of TYR, but it is regulated by end-product inhibition (Daubner et al., 2011; Tam et al., 1990), preventing large increases in catecholamine release. L-DOPA is converted into DA, resulting in an increase in DA level. In turn, DA can be converted into NE through the enzyme dopamine beta-hydroxylase (DBH; Kaufman and Friedman, 1965).

Importantly, TYR has been found to enhance neurotransmitter synthesis only in actively firing neurons (Fernstrom and Fernstrom, 2007; Lehnert et al., 1984; Tam et al., 1990). This suggests TYR can reverse a process called neurotransmitter depletion, in which increased brain activity leads to decreased DA and NE levels, with behavioral performance levels declining accordingly. This role as a depletion reverser is best illustrated by the following example. When exposed to stress or a cognitively challenging task, catecholamine neurons become more active and their synthesis rate increases (Kvetnansky et al., 2009; Lehnert et al., 1984; Mahoney et al., 2007). As more neurotransmitters are synthesized to meet the situational demands, the resource from which they are synthesized, namely TYR, is expended. Synthesis becomes limited once TYR runs low, leading to less neurotransmitter availability and corresponding decrements in performance (Goldman-Rakic et al., 2000; Muly et al., 1998). In this situation TYR might benefit brain function by providing the resources necessary to allow neurotransmitter synthesis to continue and maintain catecholamine levels needed to ensure optimal performance (Wurtman et al., 1981). On the contrary, one may assume when the rate of synthesis is not elevated then TYR supplementation amounts to providing unnecessary extra resources from which to synthesize DA and NE, which should not impact these neurotransmitters levels or their associated performance. Indeed, in rats it was shown that TYR administration only enhanced DA synthesis in the striatum when this region was pharmacologically activated (Tam et al., 1990). In other words, TYR supplementation seems to have a beneficial effect only in situations that stimulate neurotransmitter synthesis, i.e., situations that are sufficiently stressful or challenging. Indeed, in the present review we will demonstrate that TYR's role as a depletion reverser fits well with the pattern of results found in the literature.

To date there is not yet a single, agreed upon effective dose for TYR supplementation and thus administered doses have varied

Table 1
Characteristics and main outcomes of the reviewed studies.

Authors	Sample	Dose of TYR	Findings
Banderet and Lieberman (1989)	Healthy, cold exposure ($N = 23$)	100 mg/kg	Reduced symptoms, improved mood, reaction times and vigilance
Chinevere et al. (2002)	Healthy, physically exerted ($N = 9$)	150 mg/kg	No effect of TYR
Colzato et al. (2013)	Healthy, cognition challenged ($N = 22$)	2.0 g	Improved working memory
Colzato et al. (2014a)	Healthy, cognition challenged ($N = 22$)	2.0 g	Improved inhibitory control
Colzato et al. (2014b)	Healthy, cognition challenged ($N = 32$)	2.0 g	Improved convergent thinking
Deutsch et al. (1994)	Schizophrenia patients ($N = 11$)	10.0 g	Increased saccadic intrusions, no effect on behavior or cognition
Deijen and Orbleke (1994)	Healthy, auditory stress ($N = 16$)	100 mg/kg	Improved working memory and Stroop performance
Deijen et al. (1999)	Healthy, intensive combat training ($N = 21$)	2.0 g	Improved memory and tracking performance
Eisenberg et al. (1988)	ADHD patients ($N = 7$)	100 mg/kg	No effect of TYR
Gelenberg et al. (1980)	Depressive patients ($N = 1$)	100 mg/kg	Self-rated improvement of depression
Gelenberg et al. (1990)	Depressive patients ($N = 65$)	100 mg/kg	No effect of TYR
Goldberg et al. (1980)	Depressive patients ($N = 2$)	100 mg/kg	Improvement of symptoms
Growdon et al. (1982)	Parkinson's patients ($N = 23$)	100 mg/kg	Increased levels of TYR and homovanillic acid.
Kishore et al. (2013)	Healthy, heat exposure ($N = 10$)	6.5 g	Reduced delay in event related potentials
Leathwood and Pollet (1983)	Healthy, no manipulation ($N = 60$)	500 mg	No effect of TYR on mood
Lemoine et al. (1989)	Parkinson's patients ($N = 10$)	1.6–4.0 g	Improvement of symptoms
Lieberman et al. (1983)	Healthy, no manipulation ($N = 16$)	100 mg/kg	No effect of TYR on mood
Magill et al. (2003)	Healthy, sleep deprivation ($N = 76$)	150 mg/kg	Improved working memory, reasoning and vigilance
Mahoney et al. (2007)	Healthy, cold exposure ($N = 19$)	150 mg/kg	Improved working memory
Nemzer et al. (1986)	ADHD patients ($N = 14$)	140 mg/kg	No effect of TYR
O'Brien et al. (2007)	Healthy, cold exposure ($N = 15$)	300 mg/kg	Improved working memory
Palinkas et al. (2007)	Healthy, in Antarctica ($N = 43, 42$)	12 g	Improved mood during winter
Pietz et al. (1995)	Phenylketonuria patients ($N = 24$)	100 mg/kg	No effect of TYR
Pollin et al. (1961)	Schizophrenia patients ($N = 12$)	285 mg/kg	No effect of TYR
Posner et al. (2009)	ADHD patients ($N = 1$)	100 mg/kg	Improvement of symptoms
Reimherr et al. (1987)	ADHD patients ($N = 12$)	50–150 mg/kg	Short term, unsustained clinical response
Shurtleff et al. (1994)	Healthy, cold exposure ($N = 8$)	150 mg/kg	Improved working memory
Smith et al. (1998)	Phenylketonuria patients ($N = 21$)	100 mg/kg	No effect of TYR
Steenbergen et al. (2015)	Healthy, cognition challenged ($N = 22$)	2.0 g	Improved cognitive flexibility
Sutton et al. (2005)	Healthy, physically exerted ($N = 20$)	150 mg/kg	No effect of TYR
Thomas et al. (1999)	Healthy, cognition challenged ($N = 20$)	150 mg/kg	Improved working memory
Tumilty et al. (2011)	Healthy, heat exposure ($N = 8$)	150 mg/kg	Increased endurance capacity
Tumilty et al. (2014)	Healthy, heat exposure ($N = 7$)	150 mg/kg	No effect of TYR
Watson et al. (2012)	Healthy, heat exposure ($N = 8$)	150 mg/kg	No effect of TYR
Wood et al. (1985)	ADHD patients ($N = 12$)	150 mg/kg	Short term, unsustained clinical response

Studies reviewed in the present article, listing author names, publication years, type and size of sample, as well as potential stressor, dose of L-Tyrosine and the study's main outcomes. TYR, L-Tyrosine.

from 500 mg to 12 g per day (see Table 1). To put these numbers in perspective, the World Health Organization's daily upper requirement of TYR is 14 mg/kg (see Deijen, 2005), meaning an individual weighing 70 kg needs to consume approximately 1 g of TYR per day for normal functioning. Doses far exceeding 1 g are unlikely to confer any additional benefits, as the rate-limiting TH enzyme is assumed to be close to saturation under normal circumstances (Brodnik et al., 2012). Consistent with this idea, TYR transport across cell membranes decreases in healthy individuals after TYR supplementation (Wiesel et al., 1999). Any excess TYR would thus be metabolized rather than converted into L-DOPA. Future studies may wish to examine reductions in TYR transport with varying doses of TYR, to shed light on what an optimal dose might be. While too much TYR might not be extra beneficial, consuming too little might also be possible. In rats a dose of 50 but not 25 mg/kg was successful at increasing prefrontal DA level (Tam et al., 1990), although how these numbers translate to humans remains unclear. Complicating matters further, TYR shares a transporter across the BBB with several other large neutral amino-acids such as phenylalanine and tryptophan (Fernstrom, 1990). Hence the amount that crosses the BBB instead of being metabolized peripherally depends on the consumer's levels of these other amino-acids. For this reason studies investigating the effect of acute TYR supplementation should and often do have their subjects fast overnight to reduce competition from other amino-acids. This has important implications for the efficacy of TYR supplementation in a long-term setting, since completely avoiding these other amino-acids for longer periods might not be practical nor recommendable.

Such issues could be avoided by opting for L-DOPA rather than TYR administration, which acts more downstream and avoids the rate-limiting TH factor as well as the competition from other amino-acids. However there are a number of reasons why TYR supplementation might be preferable. First of all, the TH enzyme already being near saturation under normal circumstances (Brodnik et al., 2012) can be considered a positive characteristic, as it prevents large amounts of TYR being converted. In contrast, the conversion of L-DOPA into DA does not depend on such a rate-limiting factor, allowing far larger increases in catecholamines but also significantly increasing the risk of inducing levels that are detrimental for performance (Goldman-Rakic et al., 2000; Muly et al., 1998). Given the characteristic inverted-U profile of DA (Cools and D'Esposito, 2011), it would be easy for L-DOPA administration to push individuals to the lower right end of the curve, whereas the subtle increase from TYR is far less likely to do so. Given TYR's hypothesized role as a depletion reverser, it may even be that TYR maintains rather than changes an individual's position on this curve in the face of stress or cognitive demands. This also means the beneficial effects of TYR are likely smaller than L-DOPA's, especially for disorders associated with severe hypodopaminergic states. In TYR's favor, there are currently no established side-effects of long-term TYR supplementation, although one study showed increased saccadic intrusions during smooth-pursuit eye movement performance in patients with schizophrenia (Deutsch et al., 1994). On the other hand, chronic L-DOPA administration is associated with adverse symptoms such as dyskinesia, insomnia, nausea, and sometimes even psychosis (Foster and Hoffer, 2004; Liggins et al., 2012). However it should be noted studies on the chronic effect of TYR supplementation are still scarce and its potential long-term side-effects should be more extensively investigated before drawing definitive conclusions. Lastly, TYR might be preferred to L-DOPA simply because it is readily accessible to the general public, being sold in regular drug stores.

As mentioned earlier, most of the presently reviewed studies, especially those in healthy individuals, have focused on short-term effects of TYR and therefore our conclusions should mainly be considered in this context. The benefits of TYR during long-term stress are less investigated, although still promising. Prolonged stress exposure (e.g. low temperatures) can increase TH activity up to one month, suggesting TYR might be especially useful during this period. After one month, however, TH activity is no longer significantly elevated (Kvetnansky et al., 2009). Nevertheless, catecholamine neurons can remain highly active, leading to a depletion of DA and NE levels (Kvetnansky et al., 2009). This suggests TYR can also be beneficial in long-term settings. Indeed, a study in Antarctica residents (Palinkas et al., 2007) showed TYR has measurable benefits even after 7 weeks of exposure to extreme cold. Still, studies on short-term conditions far outweigh those on long-term effects and future studies should aim to lessen this discrepancy.

The available studies on TYR come from three major domains of research. First, many psychiatric disorders are associated with decreased DA and/or NE availability in the brain. Therefore, TYR has been investigated as a potential treatment for clinical symptoms associated with suboptimal catecholamine levels. Second, stress is thought to reduce catecholamine levels in the brain through increased turnover rates, leading to impairments in performance (Lehnert et al., 1984; Mahoney et al., 2007). As such, TYR supplementation has also been proposed as a potential reverser of stress-induced decrements in performance. Lastly, TYR also has promising implications for healthy individuals without overt exposure to stress, provided that high demands on cognitive performance create a stress-like state that might induce neurotransmitter depletion—the detrimental consequences of which might be counteracted by TYR supplementation (Colzato et al., 2014a; Steenbergen et al., 2015). We will use these three research areas to structure our overview, starting with studies on TYR and clinical populations, followed by studies on stressed but otherwise healthy individuals, after which we review studies on healthy humans in cognitively demanding situations. Characteristics and main outcomes of the reviewed studies are presented in Table 1.

2. Literature overview

2.1. Clinical populations

Many clinical conditions are characterized by suboptimal catecholamine levels, and this has led to the idea that TYR supplementation could alleviate catecholamine-related symptoms. Many clinical studies on TYR have concentrated on impaired DA function, whereas NE is less often investigated. Therefore the focus of this section will be on DA, while NE will be discussed only briefly.

One of the most prominent psychiatric disorders is depression and it has been linked to impaired DA and perhaps NE, function (Dunlop and Nemeroff, 2007). The possibility of using TYR as a treatment was proposed some decades ago already (Gelenberg and Gibson, 1984). This treatment was reported to help in very small samples (Gelenberg et al., 1980; Goldberg, 1980), but a larger, randomized study was unable to replicate this result (Gelenberg et al., 1990). This led to the conclusion that treating depression with TYR is not very promising (Fernstrom, 2000; Parker and Brotchie, 2011). However, depression is a complex and varied disorder that likely has many subtypes defined by different etiologies (e.g. DA versus serotonin deficiencies), as well as varying symptoms (e.g. lack of motivation versus anxiety) and these may differ per individual patient (Harald and Gordon, 2012). It is therefore unlikely a non-specific and simple treatment like food supplementation has a marked effect on samples that may be highly heterogeneous. Studies investigating the effect of TYR on depression may prove more fruitful if they take into account these different etiologies and symptoms while clearly distinguishing the

response of different patient groups. For example, we speculate perhaps those depressed individuals experiencing a lack of motivation, which may result from DA deficiency (Dunlop and Nemeroff, 2007), are the ones who could benefit most from TYR supplementation. On the other hand, individuals with psychotic depression may have excess DA, perhaps in part because their DBH enzyme, which converts DA into NE, is less active (Sapru et al., 1989). Such individuals would be unlikely to benefit from a further boost in DA activity and therefore TYR supplementation may not be recommendable for them, even though their NE levels need to be increased. Indeed, inducing higher DA levels in psychotic patients may even exacerbate their symptoms rather than improving them.

TYR supplementation might be of interest for schizophrenia, although studies on this topic are scarce. Enhancing DA function in this disorder might seem counter-productive, given it is strongly associated with increased DA signaling, sensitivity, and synthesis capacity (Howes et al., 2015; Seeman, 2013). However, in this regard it is important to distinguish between striatal areas, often demonstrating a hyperdopaminergic state in schizophrenia, and extrastriatal, prefrontal regions showing, in contrast, a marked reduction in DA activity (Davis et al., 1991; Finlay, 2001; Slifstein et al., 2015). Although not meant as a strict dichotomy, striatal hyperactivity is strongly linked to positive, i.e. psychotic symptoms, whereas prefrontal hypoactivity is associated with negative symptoms and cognitive deficits (Guillin et al., 2007). For this reason it is possible TYR supplementation could exacerbate positive symptoms by further fueling the striatum, while alleviating negative symptoms and cognitive deficits by facilitating prefrontal cortex (PFC) function. Consistent with this hypothesis, DA agonists increase psychotic symptoms in certain patients (Lieberman et al., 1987), yet they can also improve cognitive task performance (Barch and Carter, 2005; Daniel et al., 1991). Another interesting possibility is TYR's enhancement of PFC function might even downregulate the striatal hyperactivity and thereby improve positive symptoms as well. This hypothesis is based on the idea that there is strong dopaminergic reciprocity between the PFC and striatum, with increases and decreases in prefrontal DA being associated with decreases and increases in striatal DA, respectively (Akil et al., 2003; Cools and D'Esposito, 2011; Meyer-Lindenberg et al., 2005).

To date, however, the few conducted studies do not support these speculations. One study assessing the effects of 3 weeks of TYR supplementation revealed no changes in behavior (Pollin et al., 1961), although the study reported solely qualitative observations made during interviews. The only study providing quantitative data reported no effect of 3 weeks of TYR supplementation on positive or negative symptoms, nor cognitive capacity as measured by the Wisconsin card sorting test and a memory test, despite increased plasma levels of TYR (Deutsch et al., 1994). This study did reveal an increase in saccadic intrusions during smooth-pursuit eye movement performance. It should be noted both aforementioned studies examined only 11–12 individuals and, given the possible heterogeneity of schizophrenia's etiology (Tandon et al., 2008), it is unlikely the patients within and across samples were comparable to each other. Therefore, we argue it is not yet warranted to dismiss TYR's potential for alleviating symptoms of schizophrenia. Instead, more studies are needed in which samples are larger and heterogeneity is kept as small as possible or response to TYR is distinguished between patients. Other issues deserving further investigation are (1) whether TYR should be administered during periods of remission, psychosis, or both, since striatal hyperactivity seems most prominent and reliably found during psychosis (Howes et al., 2015), (2) if and how TYR supplementation interacts with DA antagonists, i.e. antipsychotics, and (3) whether a dysregulation of tyrosine transport across cell membranes (Bongiovanni et al., 2013) influences effects of TYR supplementation in patients with schizophrenia, as this dysregulation is associated with impaired cognitive function (Wiesel et al., 2005).

The third disorder we review in relation to TYR is attention deficit hyperactivity disorder (ADHD) as its etiology and symptoms strongly relate to reduced DA levels and impaired cognitive function (Del Campo et al., 2011). However, results from studies on amino-acid supplementation in ADHD are again not straightforward. Some individuals benefit from TYR (Posner et al., 2009; Reimherr et al., 1987; Wood et al., 1985), while other studies report no change in behavioral or cognitive function at all (Eisenberg et al., 1988; Nemzer et al., 1986). As is the case with depression, schizophrenia, and presumably most other psychiatric disorders, many different risk factors are associated with ADHD (Pellow et al., 2011) and they may all have different implications for potential effects of TYR supplementation. One such ADHD risk factor is impaired neurotransmitter metabolism (McConnel, 1985) and it has been proposed individuals suffering from this factor are the ones who can benefit from TYR supplementation, although they may account for only 5–10% of ADHD cases (Pellow et al., 2011). Therefore, future work on TYR and ADHD should consider these different risk factors, to elucidate whether and for whom TYR supplementation could be beneficial.

Parkinson's disease is characterized by a severe loss of dopaminergic neurons and decreased DA in many brain areas (Dauer and Przedborski, 2003), leading to impairments of behavior, emotion, and cognition. Interestingly, an early study showed administering TYR to Parkinson's patients raised levels of DA's metabolite homovanillic acid, suggesting TYR effectively promoted DA function (Growdon et al., 1982). Another early study reported clinical improvement in some, but not all patients after three years of TYR treatment (Lemoine et al., 1989). However, the reliability of the latter finding is debatable given a small sample of 10 patients was investigated and to the best of our knowledge these results have not been replicated or followed up on thus far. One reason TYR may not actually benefit every, if any, case of Parkinson's may be that the disorder is associated with reduced expression of the TH enzyme (Zhu et al., 2012), which converts TYR into L-DOPA. Low TH activity would contribute to decreased DA synthesis. If little TYR is converted into L-DOPA, then any DA deficits may not be due to a *shortage* of TYR, but rather its reduced conversion. Therefore, supplementing Parkinson's patients with TYR may amount to providing them with an unnecessary surplus of DA precursor. Furthermore, TYR stimulates neurotransmitter production only in already active neurons (Fernstrom and Fernstrom, 2007; Lehnert et al., 1984), yet Parkinson's is associated with a loss of dopaminergic neurons, thereby reducing TYR's site of action. Thus, the benefits of TYR observed in the aforementioned studies may have been either chance findings or fortunate cases in which TH expression was still relatively high. These possibilities underscore the need for considering factors such as reduced TH expression when investigating whether TYR supplementation can benefit Parkinson's patients or any other clinical population.

Lastly, TYR has also been investigated in relation to phenylketonuria, a disorder characterized by a shortage of TYR (Hanley et al., 2000). It sounds quite plausible TYR supplementation would benefit individuals suffering from this disorder, since supplementation is presumed to specifically remedy a shortage of TYR that limits neurotransmitter synthesis. However, several studies failed to find behavioral or cognitive improvements after administrating TYR to patients (e.g. Pietz et al., 1995; Smith et al., 1998) and indeed, simple TYR supplementation might not be recommendable for these patients (Van Spronsen et al., 2001). Many rationales exist for the relation between amino-acid supplementation and

phenylketonuria (Van Spronsen et al., 2010). One proposed reason why supplementation is ineffective for these patients is that their elevated phenylalanine levels compete too strongly with TYR for access through the BBB (Kalsner et al., 2001), thus preventing TYR from being converted into DA and NE. This possibility highlights the fact that compromised integrity of any step in neurotransmitter synthesis may lead to a counterintuitive effect of TYR, even when individuals have suboptimal catecholamine levels. Wherever possible, studies on TYR and clinical populations should keep in mind such limiting factors of TYR conversion.

In sum, using TYR to treat psychiatric and neurological disorders associated with suboptimal catecholamine levels is less promising and more complex than initially thought. The effect of TYR on clinical symptoms may critically depend on whether a shortage of TYR contributes to the pathology, as well as whether and how neurotransmitter synthesis is affected by the disorder.

2.2. Stressed individuals

Stress induces increased catecholamine activity and turnover rates in the brain, leading to depletion of neurotransmitter levels as well as behavioral depression (Kvetnansky et al., 2009; Lehnert et al., 1984). However, studies that administered TYR to rats prior to stress exposure have shown neurotransmitter depletion and decrements in performance can be reversed (Lehnert et al., 1984; Lieberman et al., 2005; Rauch and Lieberman, 1990; Shurtleff et al., 1993; Yeghiayan et al., 2001). These findings fueled numerous studies investigating whether and under which conditions TYR can also improve human performance during stress. These studies often focused on either physical exercise or cognitive functions.

Studies on TYR and physical exercise have primarily focused on endurance exercise, hypothesizing that maintaining adequate DA levels in the brain can support the motivation to keep on performing well. Two studies have examined TYR and endurance exercise without an additional overt stressor, but neither found any improvement following TYR administration (Chinevere et al., 2002; Sutton et al., 2005). Other studies have looked at exercise performance during heat exposure, but the results were inconsistent. One study found TYR led to longer exercise times in the absence of an increase in ratings of perceived exertion and thermal sensation (Tumilty et al., 2011), suggesting TYR enhanced endurance. However, these results were not replicated in two later studies (Tumilty et al., 2014; Watson et al., 2012). Therefore, there is no consistent evidence TYR improves physical exercise performance, e.g. endurance, during stress. In contrast, we propose physical performance *can* benefit from TYR supplementation, but only under specific conditions that activate catecholamine neurons and recruit higher cognitive functions such as attention and cognitive control. In other words, we speculate physical performance only benefits from TYR supplementation when it places high enough cognitive demands on the individual that induce catecholamine depletion. Studies showing no effect of TYR might then have examined exercise that failed to sufficiently engage cognitive processes. This hypothesis is motivated by the numerous findings that TYR is effective at enhancing cognition during stress, as discussed below.

In remarkable contrast to the aforementioned studies, TYR consistently has an effect on cognitive performance when healthy humans consume TYR prior to stress exposure. In such studies hypothermia is often used as a stressor and TYR has been repeatedly shown to reverse the impairments in cognition it may cause (Mahoney et al., 2007; O'Brien et al., 2007; Shurtleff et al., 1994). These studies investigated the crucial cognitive aspect working memory, which involves actively maintaining and updating information in memory (Baddeley and Hitch, 1974; Miyake et al., 2000). It is unsurprising working memory is often investigated in relation to TYR, given this function is closely associated with DA level (Cools et al., 2008; Goldman-Rakic et al., 2000; Moustafa et al., 2008; Siessmeier et al., 2006) and changes in catecholamine levels due to TYR are therefore likely to alter working memory performance. All studies reported cold exposure reduced working memory performance, yet this decline was reversed when subjects were supplemented with TYR. Another study looking into TYR and exposure to cold was performed by Banderet and Lieberman (1989), who considered a wider range of cognitive functions. They reported improvements in, for example, vigilance and reaction times on several tasks. Interestingly, these authors limited their analysis to "those individuals most affected by exposure to the cold" (p. 760), suggesting TYR only benefits individuals who would otherwise have been stressed by the coldness. This possibility underscores the usefulness of taking into account individual differences when investigating the effects of TYR (Jongkees et al., 2014). Furthermore, TYR has been beneficial for performance on the Stroop task and working memory while participants were exposed to an auditory stressor (Deijen and Orbleke, 1994), as well as for working memory, reasoning, and vigilance during sleep deprivation (Magill et al., 2003). Lastly, TYR has also been shown to improve both cognitive and behavioral performance in army cadets following an intensive combat training course. However, it is difficult to draw conclusions from this study, given that many other amino-acids were supplemented along with TYR and the placebo-group was not given a completely neutral placebo (Deijen et al., 1999).

Lastly, some studies have investigated whether TYR can reverse stress-induced mood decrements. Palinkas et al. (2007) supplemented TYR to residents of Antarctica, with the aim to improve mood during prolonged cold climate exposure. The adverse environment of Antarctica can be considered a multi-stressor intervention involving confinement and isolation as well as the inherent cold. Interestingly, Palinkas and colleagues found TYR improved mood, but only during the winter. This study is one of few that examines TYR supplementation in healthy individuals in a long-term setting. The result is consistent with the finding by Banderet and Lieberman (1989) that TYR reversed cold-induced reductions in mood. In contrast, TYR has been found not to influence mood without stress exposure (Leathwood and Pollet, 1983; Lieberman et al., 1983). These findings suggest TYR might be beneficial for mood, but only in stressful situations such as extreme cold.

Overall, the positive effects of TYR on cognitive performance are likely due to TYR preventing a decline of catecholamine availability during stress (Banderet and Lieberman, 1989; Kvetnansky et al., 2009; Lehnert et al., 1984), which prevents decrements in higher cognitive functions such as attention and working memory. Unfortunately, it is as of yet unclear whether these effects are attributable specifically to a modulation of DA, NE, or both. It is also still unknown what changes in cognition mediate the repletion of catecholamines and the reported improvements. For example, TYR's beneficial effect on working memory, found in many studies, might be due to TYR allowing maintenance of the optimal level of DA necessary for a balance between stable cognitive representations versus flexible updating of said representations (Cools and D'Esposito, 2011). However, this remains speculative until further investigation.

Alternatively, one study by Kishore et al. (2013) suggests at least part of TYR's mechanism of action may be enhancing NE function. They showed TYR supplementation during heat exposure had a beneficial effect on the event related potential P300 and reaction times on an auditory stimuli discrimination task. The P300 may reflect phasic activity of NE in the locus coeruleus (LC-NE) system (Nieuwenhuis et al., 2005), indicating TYR's effect on the P300 may have occurred by facilitating the function of this LC-NE system. This

is a plausible biological mechanism of the aforementioned positive effects of TYR during stress, particularly on attention and vigilance. However, it is important to keep in mind that any effect of TYR on NE is mediated by TYR's conversion into DA and therefore a role for DA in these improvements should not be excluded. Indeed, in the next section we will report evidence showing TYR also enhances functions thought to be strongly related to DA.

2.3. Cognitive demands and healthy individuals

Lastly we review studies on TYR supplementation in healthy individuals who were not explicitly and overtly exposed to stressors that may impact their performance. Instead these studies all used rather challenging cognitive tasks, which were presumed to be demanding enough to induce a stress-like state leading to neurotransmitter depletion and reduced levels of performance, an effect TYR may counteract.

Consistent with the aforementioned studies on stress, two studies to date have shown TYR can enhance working memory performance, but in the absence of an overt exposure to stress. Instead, improvements were only found under particularly challenging conditions. Specifically, Thomas et al. (1999) found TYR only promoted working memory when other tasks were performed simultaneously, a feat that would normally degrade performance. Colzato et al. (2013) found TYR improved working memory even in single-task conditions, but only in the task's more demanding condition that placed a stronger load on memory. These results confirm TYR can benefit cognitive performance and highlight the importance of a performance-degrading factor for TYR to counteract.

Aside from working memory, TYR has also been shown to selectively improve inhibitory control without influencing response execution (Colzato et al., 2014a). Furthermore, research has found TYR can promote cognitive flexibility as measured in a task-switching paradigm. In this study TYR presumably improved performance by facilitating conflict-resolving processes that may have otherwise induced a stressful state (Steenbergen et al., 2015). Recently, TYR has also been shown to promote performance on a convergent-thinking task, which is thought to rely on DA-driven cognitive control (Colzato et al., 2014b). This finding in particular points to the possibility some benefits of TYR may be mediated by enhanced DA function. None of the aforementioned studies reports an influence of TYR on mood, but this is unsurprising given that mood was not reduced even in the placebo conditions, so there was no decrement to counteract.

All in all these results suggest TYR can improve cognitive performance without overt exposure to stress, but only if performance would normally be degraded by high cognitive demands. This is likely because high cognitive demands induce a stress-like state leading to catecholamine depletion, the negative consequences of which can be counteracted by TYR.

3. Conclusion

As the biochemical precursor of DA and NE, TYR has the potential to enhance catecholamine function in the brain when situational demands are particularly high. TYR's general mechanism of action is presumably helping the brain keep up with the need for elevated rates of neurotransmitter synthesis. Unfortunately, the potential of TYR supplementation as a treatment for psychiatric disorders seems limited at best. This may be due to the fact that the suboptimal catecholamine levels in many disorders are due to an impairment of DA and/or NE synthesis and metabolism. For example, in Parkinson's disease the enzyme that converts TYR into L-DOPA is less active. Such complications limit TYR's ability to promote optimal brain function (Zhu et al., 2012). In other words, disorders characterized by suboptimal DA and NE do not necessarily benefit from TYR supplementation. The potential of TYR for improving physical exercise during stress seems equally limited; perhaps because physical performance is not as directly linked to catecholamine levels in the brain as cognitive performance is. As such we hypothesize physical exercise may benefit from TYR only to the degree that it creates a stressful state in which cognitive control functions are challenged and neurotransmitter levels are depleted. By far the clearest picture arises from studies on TYR and cognitive performance. When healthy subjects are exposed to either external stressors or cognitively demanding situations, catecholamine levels in the brain decline and performance on cognitive tasks decreases accordingly. However, TYR supplementation seems to replete neurotransmitter levels in the brain and reverse the stress-induced degradation of a variety of cognitive functions. It is not yet known whether this improvement is because of enhancement of phasic NE firing in the locus coeruleus, which would benefit functions such as attention, or due to boosting DA function in striatal or prefrontal areas, which is closely associated with working memory function. In the end it may be both, or it may differ between different cognitive functions and specific tasks of interest.

In sum, the cognitive changes mediating performance improvements after TYR supplementation remain unknown and, unfortunately, most of the literature focuses on short rather than long-term settings. Nevertheless, based on this overview of the literature we conclude TYR is very promising as an enhancer of cognition and perhaps mood, but only when (healthy) individuals find themselves in stressful or cognitively demanding situations.

Contributors

Bryant Jongkees conducted literature research and wrote the initial manuscript. Bernhard Hommel, Simone Kühn and Lorenza Colzato edited the manuscript. All authors contributed to and have approved the final manuscript.

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Conflicts of interest

None.

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