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Eating to stop: Tyrosine supplementation enhances inhibitory control but not response execution

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ABSTRACT

Animal studies and research in humans have shown that the supplementation of tyrosine, or tyrosine-containing diets, increase the plasma tyrosine and enhance brain dopamine (DA). However, the strategy of administering tyrosine (and the role of DA therein) to enhance cognition is unclear and heavily debated. We studied, in a healthy population, whether tyrosine supplementation improves stopping overt responses, a core cognitive-control function. In a double-blind, placebo-controlled, within-subject design, one hour following the administration of tyrosine (corresponding to the beginning of the 1 h-peak of the plasma concentration) or placebo, participants performed a stop-signal task—which taps into response inhibition and response execution speed. Participants in the Tyrosine condition were more efficient in inhibiting unwanted action tendencies but not in reacting to go signals. This is the first demonstration that the supplementation of tyrosine selectively targets, and reliably improves the ability to stop overt responses.

1. Introduction

Tyrosine is one of the most investigated amino acids, the building blocks of proteins. It is contained in food such as fish, soy, eggs, milk and bananas, and it is the precursor (the chemical that precedes another compound in the biochemical pathway) of the neurochemical dopamine (DA). Animal studies and research in humans have shown that the supplementation of tyrosine, or tyrosine-containing diets, increase the plasma tyrosine and enhance brain DA release, in particular from activated neurons (Acworth, During, & Wurtman, 1988; During, Acworth, & Wurtman, 1988; see Deijen, 2005, for a comprehensive review). Even though the neurobiology of tyrosine supplementation is not yet completely understood, this phenomenon does not seem to be subject to dose-dependent effects (Deijen & Orlebeke, 1994; Shurtleff, Thomas, Schrot, Kowalski, & Harford, 1994). This indicates that the relation between tyrosine and cognitive performance does not follow the inverted U-shaped dose–effect curve that is typical for dopaminergic agonists (Cools, 2006). Once the optimal level is reached, higher levels of tyrosine will thus no longer increase DA levels, as the enzyme tyrosine hydroxylase, which converts tyrosine into DA, will be inhibited (Gibson & Wurtman, 1977). Therefore, even excessive levels of tyrosine administration are not expected to impair cognitive processes.

Previous literature has mainly focused on the supplementation of tyrosine to reverse conditions associated with dopaminergic-based pathologies, such as Parkinson's disease (Growdon, Melamed, & Logue, 1982; Lemoine, Robelin, Sebert, & Mouret, 1989), phenylketonuria (van Spronsen, van Dijk, & Smit, 1996), depression (Gelenberg, Wojcik, Gibson, & Wurtman, 1983; Gelenberg & Gibson, 1984; Gelenberg, Wojcik, & Falk, 1990) and attention deficit disorder (Wood, Reimherr, & Wender, 1985; Reimherr, Wender, Wood, & Ward, 1987). Furthermore, the role of tyrosine as "counteractor" has been largely investigated under conditions that cause brain DA depletion, such as stress. In humans, tyrosine has been shown to reverse stress-induced deficits in working memory and attentional tasks (Deijen & Orlebeke, 1994; Shurtleff et al., 1994; Mahoney, Castellani, & Kramer, 2007). Only in one study tyrosine has been administered without exposure to stress, revealing beneficial effects, but only when performing more tasks at the same time (Thomas, Lockwood, Sing, & Deuster, 1999). This indicates that tyrosine may reverse "ego-depletion" (Baumeister, Bratslavsky, Muraven, & Tice, 1998) (i.e. reduced self-control after a depleting task), but only when cognitive control is required. This should not be

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surprising given that executive control is considered to emerge from the interplay between the prefrontal cortex (PFC) and the striatum, which both are driven by DA (Cools, 2006)—the precursor of which is tyrosine.

The current study focused, for the first time, on the acute effect of tyrosine supplementation on the inhibition of behavioral responses—a key cognitive control function (Logan & Cowan, 1984; Logan, 1994) that is known to be modulated by DA. Indeed, inhibitory control is enhanced after the acute intake of d-amphetamine and cocaine, drugs that stimulate DA release (Fillmore, Rush, & Abroms, 2005; Fillmore, Rush, & Hays, 2006). Along the same line, Colzato et al. (2007) reported response inhibition (assessed by means of the stop-signal task developed by Logan & Cowan, 1984) to be impaired in chronic recreational users of cocaine (Colzato, van den Wildenberg, & Hommel, 2007), who are likely to suffer from reduced dopamine D2 receptors in the striatum (Volkow, Fowler, & Wang, 1999). Participants pressed a left or right button as soon as a green left- or right-pointing arrow appeared (go trials). However, in some trials the color of the arrow suddenly changed to red, in which case the participants were supposed to refrain from responding (stop trials). This stop-signal task measures both the efficiency of response execution (by means of reaction time to go-signals) and the efficiency in inhibitory control (by means of the stop signal reaction time or SSRT, where longer SSRT reflect general slowing of inhibitory processes and indicate a lower level of inhibitory efficiency). Cocaine users needed significantly more time to inhibit responses to stop-signals than non-users.

Given the role of DA in modulating response inhibition, we expected the supplementation of tyrosine to enhance stopping control. Moreover, based on the ego-depletion hypothesis (Baumeister et al., 1998), we expected this effect to be limited to stopping overt responses without affecting response execution speed. Demanding tasks, such as stopping on time, may deplete the available control resources more than easy tasks, such as reacting to go signals. Accordingly, we assumed tyrosine to be able to replete the missing resources when more control is needed to carry out the task, as in the case of inhibiting unwanted action tendencies.

2. Experimental procedures

2.1. Participants

Twenty-two healthy female adults (mean age=20.4 years; mean Body Mass Index=21.5) with no cardiac, hepatic, renal, neurological or psychiatric disorders, personal or family history of depression, migraine and medication or drug use participated in the experiment and served in two experimental sessions separated by 3–7 days. A double blind, placebo-controlled, randomized cross-over design with counterbalancing of the order of conditions was used to avoid expectancy effects. Placebo and L-Tyrosine dose corresponded to oral dose (powder) of 2.0 g of microcrystalline cellulose (Sigma-Aldrich Co. LLC) and of 2.0 g of tyrosine (supplied by Bulkpowders Ltd.) dissolved in 400 ml of orange juice. Following Markus, Firk, Gerhardt, Kloek and Smolders (2008), women using contraception were tested when they actually used the contraception pill. On each experimental morning, participants arrived at the laboratory at 9:30 a.m. Participants had been instructed to fast overnight; only water or tea without sugar was permitted. In addition, subjects were not allowed to use any kind of drugs before and during the experiment or to drink alcohol the day before their participation and arrival at the laboratory. Written informed consent was obtained from all subjects; the protocol and the remuneration arrangements of 20 euro were approved by the local ethical committee (Leiden University, Institute for Psychological Research).

2.2. Apparatus and stimuli

The experiment was controlled by a ACPI uniprocessor PC running on an Intel Celeron 2.8 gHz processor, attached to a Philips 109B6 17 in. monitor (LightFrame 3, 96 dpi with a refresh rate of 120 Hz). Responses were made by pressing the "Z" or "?" of the QWERTY computer keyboard with the left and right index finger, respectively. Participants were required to react quickly and accurately by pressing the left and right key in response to the direction of a left- or right-pointing green arrow (go trials) of about $3.5 \times 2.0\ cm^2$ with the corresponding index finger.

2.3. Stop-signal task

Each experimental session consisted of a 30-min session in which participants completed a version of the stop-signal task adopted from Colzato et al. (2007), Colzato, van den Wildenberg, van der Does, & Hommel, 2010; Colzato, van den Wildenberg, & Hommel, 2013). Arrows were presented pseudo-randomly for maximal 1500 ms, with the constraint that they signaled left- and right-hand responses equally often. Arrow presentation was response-terminated. Intervals between subsequent go signals varied randomly but equiprobably, from 1250 to 1750 ms in steps of 125 ms. During these interstimulus intervals, a white fixation point (3 mm in diameter) was presented. The green arrow changed to red on 25% of the trials, upon which the choice response had to be aborted (stop trials). A staircase-tracking procedure dynamically adjusted the delay between the onset of the go signal and the onset of the stop signal to control inhibition probability (Levitt, 1971). After a successfully inhibited stop trial, stop-signal delay in the next stop trial increased by 50 ms, whereas the stop-signal delay decreased by 50 ms in the next stop trial when the participant was unable to stop. This algorithm ensured that motor actions were successfully inhibited in about half of the stop trials, which yields accurate estimates of SSRT and compensates for differences in choice RT between participants (Band, van der Molen, & Logan, 2003). Individual SSRTs were calculated according to the *integration method* (see Logan & Cowan, 1984, see Fig. 1). The stop task consisted of five blocks of 104 trials each, the first of which served as a practice block to obtain stable performance.

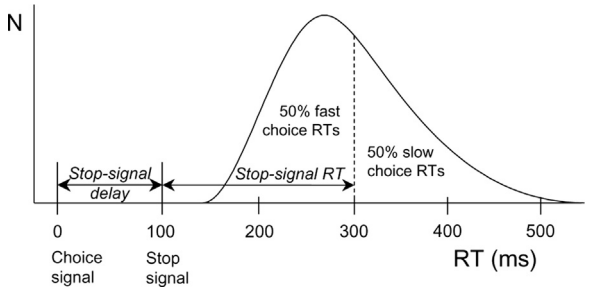

Fig. 1. Calculation of stop-signal RT (SSRT) according to a race model. Following the race model assumption of independence (Logan & Cowan, 1984), the RT distribution of the go process is the same whether or not a stop signal is presented. The left side of the go RT distribution represents fast responses that escape inhibition. The right side represents slow responses that will be inhibited. If participants failed to stop on *n*% of the stop trials (here 50%), the finishing time of the stop process was on average equal to the *n*th percentile of the go RT distribution (here 300 ms). The mean stop signal delay (SSD, 100 ms) was then subtracted from the nth percentile of the go RT distribution, resulting in the estimate of the mean SSRT (200 ms).

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