



Tryptophan

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Introduction

Common sense says that “you make a living by what you get but you make a life by what you give.” Prosocial behavior has been defined as voluntary acts intended to help or benefit others, for example, by helping or donating (Penner et al. 2005).

Notably, augmented serotonin (5-HT) levels in the brain have been associated to social behaviors like cooperation and affiliation (for reviews see Crockett 2009; Kiser et al. 2012). On the contrary, 5-HT dysfunctions have been observed to be linked with violent criminal, impulsive, and antisocial behaviors (Coccaro et al. 2015).

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Given the link between social behavior and 5-HT function, it is very plausible that impacting 5-HT levels could result in beneficial changes in prosocial behavior. One way of impacting 5-HT levels is supplementing its chemical forerunner tryptophan (TRP). Given that the human body cannot synthesize TRP itself, TRP is considered an essential amino acid because it is derived from the diet. Interestingly, TRP can augment 5-HT synthesis in rats (Yuwiler 1973) and humans (Bowers 1970). Accordingly, several studies have examined whether the supplementation of TRP can have a positive impact on social behavior that depends on serotonergic function (Crockett 2009; Kiser et al. 2012).

Nonetheless, outcomes from TRP studies have not been completely clear-cut and several factors—such as individual differences—might regulate the effect of TRP on prosocial behavior. In this chapter, adapted from Steenbergen et al. (2016), we will first describe how TRP supplementation impacts 5-HT function. Second, we will outline the available studies on TRP and prosocial behavior. The focus will be on healthy humans with supposedly normal 5-HT levels and not on humans with psychiatric disorders and/or showing antisocial behaviors associated with decreased or dysfunctional 5-HT availability in the brain. The studies in healthy humans point out that TRP has promising potential for promoting social behavior, in particular prosocial and agreeable behavior. Last, we will identify potential modulators of response to TRP supplementation.

Mechanism of Action

TRP plasma levels rise after TRP intake (Yuwiler et al. 1981). The enzyme tryptophan-hydroxylase (TPH), which converts TRP into 5-HT, is accountable for managing the rate at which TRP is transformed into 5-HT (Silber and Schmitt 2010; Young and Gauthier 1981), see also Fig. 1. Notably, the dose of 3 g is enough to saturate TPH and to double the rate of 5-HT synthesis (Young and Gauthier 1981).

On the contrary to other large neutral amino acids (LNAA) such as valine, leucine, tyrosine, isoleucine, and phenylalanine, TRP is the amino acid that is least abundant in protein (Wu 2009). Therefore, a diet rich in protein will cause reduced increments in TRP plasma levels than in the plasma levels of other LNAAs (for an exhaustive elucidation see Le Floc'h et al. 2011). Additionally, all LNAAs have to be transported through the blood–brain barrier by the same transport system. That is, the LNAAs compete for transport across the blood–brain barrier, which restrains uptake of TRP in the brain (Fernstrom 1990, 2013). Remarkably, as a consequence of this phenomenon, brain TRP and 5-HT levels could actually drop when TRP intake happens together with other LNAAs (Fernstrom and Faller 1978). Nonetheless, the consumption of pure TRP causes a substantial rise in plasma TRP levels and the TRP:LNAAs ratio at approximately 60 min after supplementation. Two hours after administration peak plasma and TRP:LNAAs levels are obtained after consumption and stay high for at least 7–12 h (Markus et al. 2008; Yuwiler et al. 1981).

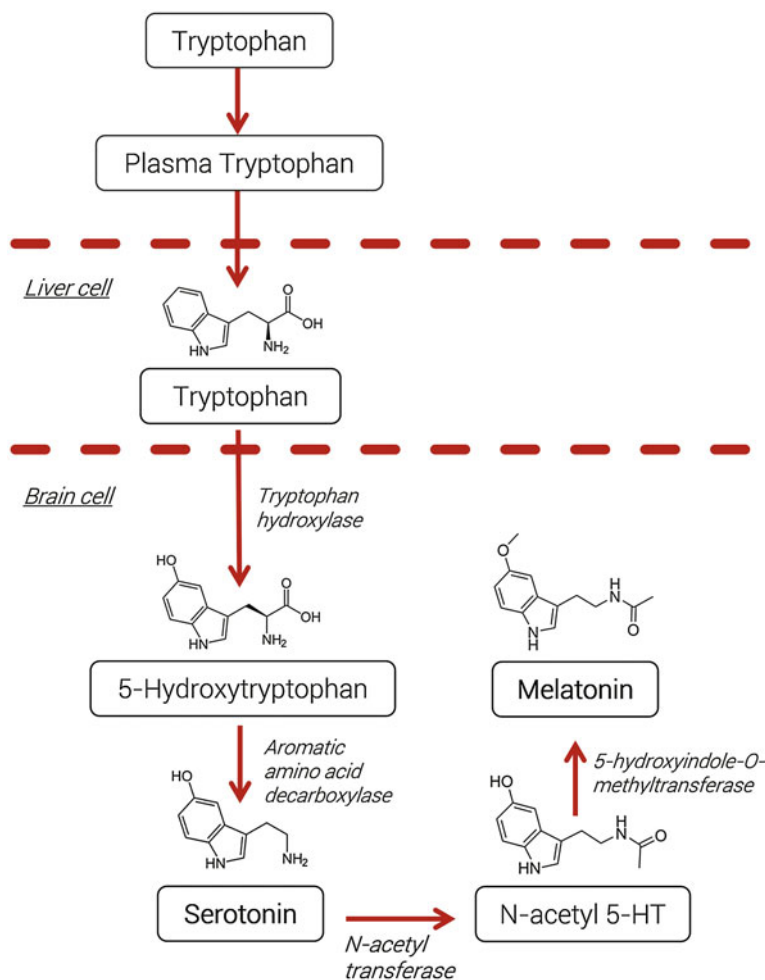


Fig. 1 Schematic representation of the effect of acute tryptophan supplementation on tryptophan to serotonin conversion. Once it has passed the blood–brain barrier, the enzyme tryptophan-hydroxylase converts tryptophan into 5-hydroxytryptophan. In a second step, 5-hydroxytryptophan is converted, via the enzyme aromatic amino acid decarboxylase, into serotonin leading to an elevation in serotonin level. In further steps, serotonin is then converted into melatonin

It has been found that doses up to 5 g of TRP per day do not lead to any harmful effects (Hiratsuka et al. 2013). Only one long-term study, in which the dose of 3 g daily for 3 weeks was supplemented, revealed side-effects (dizziness and epigastric pain) of TRP consumption, even though these conditions were also detected before the start and during the run-in placebo week of the study (Thomson et al. 1982). In contrast, in another long-term study in which 3 g TRP daily was provided to experimental subjects for 12 weeks, only one subject reported diarrhea as a side-effect (Van Praag et al. 1972). The above-mentioned side-effects are more

probable to arise when higher doses are used (i.e., 70–200 mg/kg; for a review see Fernstrom 2012). The amount and diversity of described side-effects increments when higher doses are supplemented over longer periods (e.g., 6 g daily for 3 months; Steinberg et al. 1999). This is not surprising if we consider that TPH enzyme saturates already at a dose up to 3 g (Young and Gauthier 1981), pointing out that doses higher than this will not lead to any further enhancement of 5-HT function. Finally, when TRP is supplemented jointly to drugs known to increase 5-HT functioning such as certain antidepressants, side-effects such as nausea, tremor, dizziness, and drowsiness may occur (Fernstrom 2012).

A dominant hypothesis in explaining the cognitive mechanisms behind the effects of TRP on social behavior in healthy humans relies on the fact that through its impact on the serotonergic system, TRP might induce a selective bias toward positive information. Indeed, enhanced 5-HT levels—obtained via repeated supplementation of TRP or the selective serotonin reuptake inhibitor citalopram—are linked with reduced attentional vigilance toward negative words (Murphy et al. 2006), reduced fear recognition (Harmer et al. 2006), increased recognition of happy faces (Murphy et al. 2006) and increased mood intensity rating (Gibson et al. 2014). However, unfortunately, not every study has confirmed a selective bias toward positive information with high 5-HT. For example, Attenburrow et al. (2003) showed intake of TRP increased the recognition of both happiness and fear. Nonetheless, it seems clear from these studies that TRP administration, alike to antidepressants that enhance 5-HT levels (Harmer 2008), might lead to “positive re-biasing in information processing,” causing more attentiveness to positive stimuli. We suggest that such a bias could promote more positive social behaviors such as affiliation and cooperation.

Enhancing Prosocial Behavior in Healthy Humans

The studies in healthy humans described in this section point out to the role of TRP as a promising tool for promoting prosocial behavior. A placebo-controlled study by Aan het Rot et al. (2006) showed that the administration of TRP (1 g, 3 times a day for 15 days) promoted agreeable behavior and perceptions of agreeableness and decreased quarrelsome behavior.

Economic decision-making tasks such as the trust game (Camerer and Weigelt 1988) and the ultimatum game (Güth et al. 1982) have been found to be affected by TRP administration. These economic games include important key processes connected to social behavior such as altruism, empathy, fairness, and cooperation (Ebstein et al. 2010). For example, TRP administration seems to enhance interpersonal trust as indexed by a trust game—a task that measures the extent to which one person (the truster) trusts another person (the trustee), as measured by money units transferred from truster to trustee (Camerer and Weigelt 1988). In agreement with the idea that TRP administration might promote agreeable and prosocial behavior, after the acute intake of 0.8 g TRP, participants transferred significantly

more euros to the trustee than after ingestion of the placebo, an index of augmented interpersonal trust (Colzato et al. 2013). In line with this outcome, charitable donating was enhanced after acute TRP administration (0.8 g). Participants almost doubled the amount of money participants donated to charity, as compared to the placebo condition (Steenbergen et al. 2014).

A recent study by Cerit et al. (2015), in which participants received 2.8 g of TRP or placebo for 6 days, found no significant effect of TRP on behavior in the ultimatum game. In this task, participants are usually asked to make a proposal about the allocation of money among the participant and another player, and/or to accept or reject a proposal by another (sham) participant. The ultimatum game measures the trade-off between decisions driven by fairness versus selfishness. If the proposal is not accepted, both players do not obtain any money. An additional analysis in the study by Cerit et al. (2015), in which seven participants who accepted all offers post-intervention were omitted, pointed out to an increment in rejections of very unfair offers in the TRP group compared the placebo group. As suggested by the authors, this outcome seems to dispute the idea that TRP can enhance prosocial behavior, even though it may be due to the fact that on the testing day TRP has not been administered to the participants. Indeed, according to the authors, this may have lead to a relative depletion as compared to previous days, hence, causing a similar result that one would anticipate as a consequence of TRP depletion (Crockett et al. 2008). Nonetheless, an issue arguing against this possibility is that, within the same study, TRP administration was also found to diminish the physiological response to stress (i.e., reduced cortisol level; for consistent results, see also Cerit et al. 2013). Given that cortisol responses are strongly related to the automatic processing of emotional information (Ellenbogen et al. 2010), with lower cortisol responses indicating less reactivity to stressors, the outcomes by Cerit et al. (2013, 2015) of the lower cortisol response to stressors following TRP, might suggest that TRP supplementation indeed induced a positive bias in information processing. An intriguing alternative interpretation of the outcome that TRP supplementation increased instead of reduced rejection rates is linked to the idea that reciprocity is important for cooperation, which consists of a combination of altruistic rewarding and altruistic punishment (i.e., imposing sanctions on others who violate norms; Fehr and Fischbacher 2003). Hence, if one considers the rejection of unfair offers as an index of altruistic behavior, i.e., altruistic punishment, then an increment of rejections after TRP can in fact reflect a form of prosocial behavior.

Finally, in an unpublished naturalistic pilot study on 292 individuals Peter Kirsch and colleagues at the German central institute of mental health in Mannheim could demonstrate that participants with a TRP rich nutrition regime show better social cognitive performance as measured by the Reading the Mind in the Eyes task.

In sum, these results described above suggest that TRP administration, via augmented 5-HT functioning, has promising potential to promote positive social, i.e., agreeable, prosocial behavior.

TRP Effectivity Depends on Variety of Factors

As pointed out in the Introduction, TRP effects on 5-HT synthesis and functioning seem to rely on several factors, such as the competition between LNAAs (see Section “[Mechanism of action](#)”), neuronal activity, enzymatic activity, genetic variability, gender, age and the amount of TRP contained in one’s diet (Young 2013). All these factors may contribute in elucidating part of the variability in TRP effectivity, both within and between individuals.

At least in animals, it has been found that the consumption of TRP diminishes the firing rate of serotonergic neurons (Trulsson and Jacobs 1976). Notably, this is also the case for the supplementation of selective 5-HT reuptake inhibitors, which are assumed to augment 5-HT availability in the synapse (Fischer et al. 2015). Varying serotonergic levels by means of TRP administration is most likely to modulate the rate of 5-HT release when neurons are firing at a high rate (Trulsson and Jacobs 1976). This suggests that effects of TRP supplementation might be most compelling in conditions under which the firing rate of 5-HT neurons is augmented, for example, when exhibiting a high level of behavioral arousal (Young 2013; Young et al. 1988), which, at least in animals, has been shown to regulate the amount of release of 5-HT (Rueter et al. 1997).

Given that TPH enzyme is critical to the conversion of TRP into 5-HT, it is crucial to take into account that this conversion happens in two locations through two different types of enzyme: the gut (TPH1) and the brain (TPH2) (Walther et al. 2003). As 5-HT cannot pass the blood–brain barrier while TRP can, all available 5-HT in the brain relies on the conversion of TRP to 5-HT by TPH2 after TRP has passed the blood–brain barrier. Therefore, if the TPH1 enzyme in the gut is very active, more TRP is converted there and less will be available to pass through the blood–brain barrier and be converted into 5-HT in the brain. Consequently, TRP might have less effect on social behavior in individuals with highly active TPH1 enzyme.

Another factor that increases variability in the effectiveness of TRP supplementation may be vitamin B and D availability. As a matter of fact, activation of the TPH2 enzyme, involved in the first step of the conversion of TRP into 5-HT in the brain (Gutknecht et al. 2009; Walther et al. 2003), relies on vitamin D hormone availability (Haussler et al. 2011). Likewise, the decarboxylase enzyme involved in the last step of the conversion of TRP in 5-HT needs vitamin B6 (pyridoxine) as a cofactor in order to convert 5-HTP into 5-HT. Hence, even though vitamin B6 is not a chemical forerunner of 5-HT, it can be regarded as a rate-limiting factor in the final step of 5-HT synthesis (Deac et al. 2015). To that end, it is frequently advised to take vitamin B and D supplements together with TRP. It is not to exclude that TRP might have decreased effectivity in individuals with deficient vitamin B and D levels.

Moreover, variations in genes linked with serotonergic functioning might play a part in inter-individual variability in response to TRP. Even though the exact role of the A-C polymorphism of the TPH gene in the activity of TPH is unclear, it seems

to play a crucial, functional role. A-carriers (A2051C) have lower levels of 5-HIAA, the main metabolite of 5-HT, as compared to C-carriers (Chen et al. 2010), indicating decreased 5-HT transmission. Furthermore, A-carriers (A218C and A779C) exhibit higher levels of aggression and explicit anger (Hennig et al. 2005; Manuck et al. 1999; Reuter and Hennig 2005). These outcomes point to two opposing hypotheses concerning the potential effect of this polymorphism on TRP effectivity. For once, A-carriers displayed high levels of aggression and explicit anger, indicating much room for enhancement after TRP supplementation. Then again, their decreased 5-HT activity might actually cause less impact of TRP based on the hypothesis that TRP is particularly effective when the firing rate of serotonergic neurons is elevated. At this point, it is not yet clear if and in which direction this polymorphism predicts response to TRP supplementation and more research is needed to answer this question.

Another potential source of TRP effects is inter-subject and inter-sample variability in several factors. For example, variation in body mass index (BMI) might induce different substance concentration levels when the same dose is administered to all participants. Notably, none of the above-discussed studies included individualized dosages. It would be interesting to investigate whether individual differences in TRP effectivity might perhaps be predicted by an individual's BMI. The use of individualized dosages (e.g., a dosage of X mg per kg of bodyweight instead of the same dosage for everyone) might increase the chance to validate consistent and replicable findings with TRP. Furthermore, gender might affect the efficacy of TRP supplementation, since 5-HT synthesis seems to be lower in females than in males (Nishizawa et al. 1997). Along the same line, TRP depletion lowered mood in women but not in men (Ellenbogen et al. 1996). Moreover, age can significantly modulate both serotonergic functioning and (pro)social behavior. For example, aging has been linked to increments in 5-HT availability, receptors, transporters, and enzymes (Fidalgo et al. 2013). Likewise, at least in animals, aging and age-related diseases are linked with unbalanced TRP metabolism (Van der Goot and Nollen 2013).

Finally, we would like to emphasize the importance of baseline levels of social behaviors or related measures. This idea is based on the outcome of Crockett et al. (2010), who found citalopram only modulated moral judgments in those who exhibited higher baseline empathy levels. Considering that one way by which TRP could operate is via the biasing of information processing toward positive stimuli, this implies that in individuals with low 5-HT, the initial bias toward negative stimuli might be greatest and hence they could benefit most from an increase in 5-HT. Nonetheless, support for a relation between TRP efficacy and initial 5-HT state is still controversial (Silber and Schmitt 2010). Connected to the previous issue, substantial research is necessary to explore the possible long-term effects of TRP. This matter is particularly crucial when placebo-controlled within-subjects designs are implemented, as it may help to set the adequate distance between two or more critical sessions.

Conclusion

As the chemical forerunner of 5-HT, TRP has the potential to increase serotonergic function in the brain. TRP seems to be a promising means for promoting prosocial behavior such as agreeableness, sharing, helping, donating in healthy humans. This implies TRP supplementation to be a useful tool to enhance positive social functioning in inexpensive and efficient ways.

TRP, via stimulating 5-HT synthesis, is likely to operate by inducing a positive bias in information processing, causing more attentiveness to positive stimuli and, therefore, less negative (e.g., aggressive), social behavior. It is essential to take into account that, aside from inducing a bias in information processing, the modulating effect of TRP on social behavior might also be mediated by other pathways. For example, TRP supplementation and increments in brain TRP are also related with better quality of sleep and better mood (for a review see Silber and Schmitt 2010), factors which might affect behavior in several ways. The connection between TRP and quality of sleep is very likely if one bears in mind that 5-HT is also the precursor of melatonin, which plays an important role in managing the sleep-wake cycle (Richardson 2005). Moreover, TRP is regarded to have a mild sedative effect, possibly due to the increment in melatonin production linked with the rise in 5-HT levels (Bravo et al. 2012). Such a connection may elucidate, for instance, the beneficial effects that TRP can have on impulsive behavior (Silber and Schmitt 2010).

The link between TRP and mood may illustrate an alternative pathway via which TRP can modulate social behavior. As suggested by Young (2013), given that increments in 5-HT may have beneficial effects on mood (Bravo et al. 2013), and as better mood is typically linked to more positive social interactions, the effects of TRP in enhancing prosocial behavior may just be the results of better mood following TRP ingestion.

Another important aspect regards the fact that TRP can be metabolized not only via the 5-HT pathway but also via the kynurenine pathway. As pointed out by Steenbergen et al. (2016), De facto, outside the central nervous system, only one percent of dietary TRP is converted into 5-HT. This means that the majority of TRP is catabolized along the kynurenine pathway (Russo et al. 2003). In the first step of this metabolic way, TRP is transformed into kynurenine. Subsequently, kynurenine is converted to a series of metabolites, such as 3-hydroxykynurenine and quinolinic acid (for a detailed explanation of this oxidative pathway, see Russo et al. 2003). Notably, kynurenine can pass the blood-brain barrier and prompt the production of neuroactive metabolites that affect glutamatergic and cholinergic signaling. This fact indicates that TRP effects are not modulated solely by 5-HT. This might be specifically relevant for females afflicted by irritable bowel syndrome, as they show an increase of TRP catabolism along the kynurenine pathway, which contributes to the abnormal 5-HT functioning in this syndrome (Fitzgerald et al. 2008). Therefore, considering individual differences in TRP metabolism (e.g., the amount of TRP metabolized via the kynurenine pathway vs. via the 5-HT pathway) may offer important understandings into the effectivity of TRP in modulating social behavior.

In sum, even though more research is needed to disentangle and understand the relation between individual differences, TRP effectivity, 5-HT functioning, and social interactions, we suggest that TRP can be an effective tool in enhancing prosocial behavior in healthy humans.

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