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# Acute Phenylalanine/Tyrosine Depletion: A New Method to Study the Role of Catecholamines in Psychiatric Disorders

Sean P. Barrett, BA, and Marco Leyton, PhD

## Focus Points

- Acute phenylalanine/tyrosine depletion (APTD) is a recently developed technique that is thought to safely, rapidly, and transiently reduce the production of the catecholamine neurotransmitters dopamine and norepinephrine in the brain.
- APTD has been shown to alter motivation, drug-related responses, and mood in healthy individuals, as well as manic symptoms in patients with bipolar disorder.
- A variation of the APTD technique may be appropriate for extended clinical use.

## Abstract

*The acute phenylalanine/tyrosine depletion (APTD) method was recently developed as a new tool to transiently decrease catecholamine transmission in humans. Initial studies indicate that the treatment is safe, well tolerated, and effective. Studies in primates suggest that both dopamine and norepinephrine synthesis are decreased, and it might be possible to separate these effects. Behavioral effects appear to develop rapidly, within 3 hours in some studies. Preliminary findings in healthy individuals suggest that APTD can lead to a mild mood-lowering effect associated with decreased interest in both natural and drug rewards. In bipolar patients, more pronounced effects may be elicited, and manic symptoms might be reduced. A variant of this technique is being developed that would be suitable for extended administration, and an initial study suggests that it could have clinical utility as a treatment augmentation strategy for hyper-dopaminergic disorders.*

## Introduction

The catecholamine neurotransmitters dopamine (DA) and norepinephrine (NE) are thought to contribute to the regulation of attention, arousal, mood, and motivational states.<sup>1</sup> Disturbances to this catecholaminergic regulation might increase vulnerability to various forms of psychopathology, including attention-deficit/hyperactivity disorder (ADHD),<sup>2</sup> mood disorders,<sup>3</sup> and substance abuse.<sup>4</sup> However, most of the evidence supporting these asso-

ciations comes from indirect sources, such as correlations between symptoms and peripheral markers, and pre-clinical evidence that effective medications affect catecholamine transmission. Direct evidence for causal associations is generally sparse. One of the primary obstacles to a more direct assessment of the roles of DA and NE in psychiatric disorders has been the lack of an effective tool that safely, rapidly, and selectively decreases catecholamine function in humans. In

the present review, we describe recent efforts to develop a tool that might fit these needs, acute phenylalanine/tyrosine depletion (APTD).

## The Catecholamine Metabolic Pathway

The synthesis of catecholamines in the brain occurs in several steps (Figure). The amino acid precursors of DA and NE, phenylalanine and tyrosine, are derived from dietary protein. Neither crosses the blood-brain barrier passively. Instead, competition for active transport into the brain occurs via a saturable system that is also used by other large neutral amino acids. Once phenylalanine and tyrosine are in the brain and taken up into catecholamine neurons, there are three enzymatic steps. First, phenylalanine hydroxylase converts the essential amino acid phenylalanine into tyrosine, thereby providing an endogenous source of the latter amino acid. Second, tyrosine hydroxylase adds a hydroxyl group to tyrosine to produce 3,4-dihydroxy-L-phenylalanine (L-DOPA). L-DOPA is then rapidly converted into DA by aromatic amino acid decarboxylase and moved into storage vesicles by the vesicular monoamine transporter. In noradrenergic neurons, these vesicles contain DA- $\beta$ -hydroxylase, the enzyme that converts DA into NE.

The conversion of tyrosine to L-DOPA is considered the rate-limiting step in catecholamine synthesis. Tyrosine hydroxylase is the slowest of the metabolic pathway's three enzymes, and

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under normal physiological conditions it is incompletely saturated. As a consequence, reducing tyrosine availability should reduce catecholamine synthesis. A growing body of evidence indicates that APTD is a safe, rapid, and effective means for accomplishing this.

**APTD Validation Studies**

Ingestion of an amino acid load can induce protein synthesis. Since the APTD mixture lacks phenylalanine and tyrosine, these amino acids must be derived from the body's stores, resulting in a reduction in their plasma concentrations. Moreover, since APTD mixtures contain other large neutral amino acids, the competition for transport across the blood-brain barrier is also increased,<sup>5</sup> further reducing the amount of phenylalanine and tyrosine in the brain.<sup>6,7</sup>

Recent studies provide compelling evidence that depletion of phenylalanine and tyrosine in the brain leads to decreased DA synthesis. In research animals, APTD decreases postmortem

tissue concentrations of DA,<sup>8</sup> amphetamine-induced DA release,<sup>8</sup> cerebrospinal fluid (CSF) concentrations of the DA metabolite homovanillic acid,<sup>9</sup> and amphetamine- and cocaine-induced behavioral activation.<sup>10</sup> In humans, APTD increases circulating levels of prolactin,<sup>11</sup> a neuroendocrine index of decreased DA transmission, as well as [<sup>11</sup>C]raclopride binding, a more direct functional neuroimaging measure of decreased DA levels in striatal synaptic clefts.<sup>12,13</sup> In the two positron emission tomography (PET) studies,<sup>12,13</sup> the APTD-induced change in [<sup>11</sup>C]raclopride binding correlated with the reductions in phenylalanine and tyrosine, suggesting a direct association between DA release and precursor availability.

Less is known about the effects of APTD on NE. In nonhuman primates, APTD has been reported to decrease CSF concentrations of the NE metabolite, 3-methoxy-4-hydroxyphenethyl-ene glycol, to the same degree that it reduces homovanillic acid.<sup>9</sup> In com-

parison, studies in rats suggest a more selective effect on DA.<sup>8</sup> It remains unclear whether this reflects a difference between rodents and primates, a failure as yet to identify the locus of effect on NE, or differences in the APTD mixtures used by the two research groups. Very preliminary evidence suggests that, in humans, it may be possible to distinguish between effects of APTD that are DA versus NE mediated based on whether they are prevented by the immediate DA precursor, L-DOPA. Considering that L-DOPA may selectively increase DA synthesis,<sup>14,15</sup> it may reverse DA-related effects of APTD while leaving NE-related effects intact.

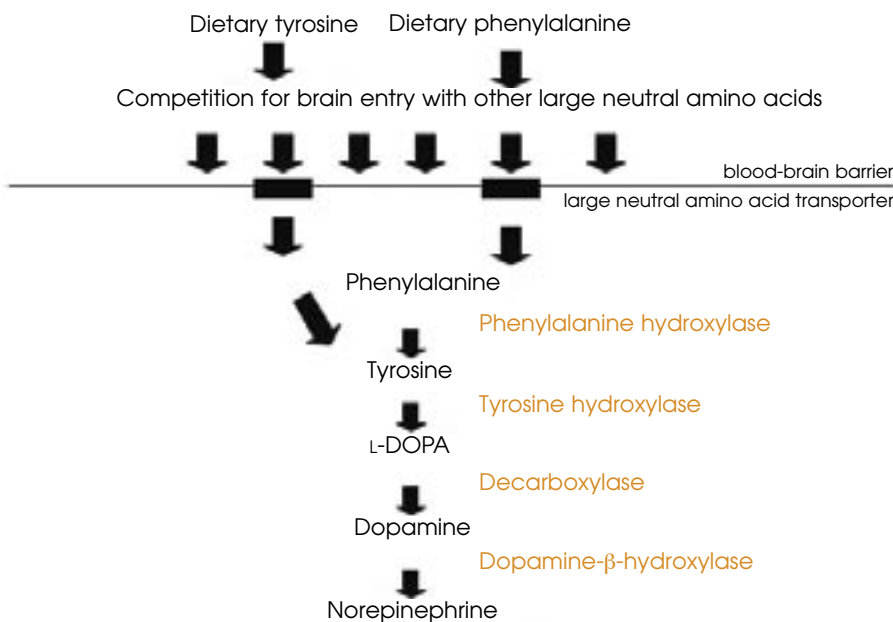
There are currently two different versions of the APTD mixture in use; one containing 14 amino acids,<sup>5</sup> and the other only 7.<sup>8</sup> Although these methods have yet to be directly compared, each has been successfully used to examine aspects of catecholamine functioning in humans.<sup>12,13</sup> Both mixtures are believed to transiently reduce catecholamine synthesis via the same mechanisms and over a similar time course.<sup>16,17</sup> Effects of the APTD mixtures have been observed within 3 hours of administration, and their total duration of action is thought to be <8 hours. They can therefore be used on an outpatient basis and do not require prolonged monitoring.

In addition, APTD has been demonstrated to be well tolerated in both clinical and normal human populations,<sup>5,16</sup> and it appears to be devoid of any serious side effects, such as the motor dyskinesia often associated with other treatments that reduce catecholamine transmission. Moreover, while numerous medications are available that bind to one or more of the multiple DA and NE receptor subtypes, these compounds tend to be nonspecific, also binding to the receptors of noncatecholaminergic transmitter systems.<sup>18</sup> In comparison, with the possible exception of effects on some trace amines, APTD is thought to act specifically on catecholamine synthesis and reduce transmitter binding at all DA and NE receptor subtypes.

**Behavioral Effects of APTD in Humans**

Behavioral effects of APTD are now being examined in both healthy and

**Figure**  
**The Catecholamine Metabolic Pathway**



The catecholamine amino acid precursors phenylalanine and tyrosine are obtained from dietary sources. They compete with other large neutral amino acids for access to a saturable transporter that actively carries them across the blood-brain barrier. Once taken up into catecholamine neurons, phenylalanine undergoes two hydroxylations, first by phenylalanine hydroxylase and then by tyrosine hydroxylase, to produce 3,4-dihydroxy-L-phenylalanine (L-DOPA). L-DOPA is rapidly converted into dopamine by aromatic amino acid decarboxylase. In norepinephrine neurons, the storage vesicles contain dopamine-β-hydroxylase, which converts dopamine into norepinephrine. The rate-limiting enzyme in catecholamine synthesis is tyrosine hydroxylase.

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clinical populations (Table).<sup>5,11,16,17,19-23</sup> Although this is still a relatively new area of investigation, preliminary evidence suggests that APTD can affect motivation, reinforcement, and mood.

### Motivation and Reinforcement

The catecholamines, particularly DA, have been implicated in various motivational processes. For example, in various laboratory animal species, DA-specific lesions interfere with appetitive behaviors directed toward normally reinforcing stimuli, including food,<sup>24</sup> sexual partners,<sup>25</sup> and abused drugs.<sup>26</sup> Such findings were initially interpreted as implicating DA in the pleasure associated with reward.<sup>27</sup> However, due largely to evidence that DA transmission is also increased during stress,<sup>28</sup> exploratory behavior,<sup>29</sup> and expectation of reward,<sup>30</sup> a revised view is that DA is more closely related to the motivation to interact with biologically-relevant environmental stimuli.<sup>31</sup> This possibility has been explored in recent APTD studies.

In healthy men and women, APTD has been reported to increase feelings of boredom<sup>5</sup> and apathy,<sup>19</sup> possibly reflecting a generalized indifference to otherwise interesting or important environmental stimuli. Consistent with this interpretation, APTD decreased the salience of rewarding cues in a decision-making task<sup>19</sup> and diminished the ability of the ADHD medication *d*-amphetamine to enhance responding for monetary reward.<sup>20</sup> The effect of APTD on reinforced learning was prevented by L-DOPA, suggesting further that it is a DA-mediated effect.<sup>20</sup>

### Drug-Related Motivation

Animal models of addiction have long implicated DA in the addictive properties of numerous abused substances, including cocaine, amphetamine, alcohol, and nicotine.<sup>4,26,31</sup> Each of these substances promotes midbrain DA neurotransmission, and disruption of this action interferes with drug self-administration.<sup>26,31</sup> Moreover, following repeated drug exposure, environmental

cues that predict drug availability gain the ability to increase DA release.<sup>32</sup> Preventing cue-induced DA transmission decreases drug-seeking behavior.<sup>33</sup> In comparison, disrupting DA transmission does not appear to diminish the hedonic effect of rewards.<sup>31</sup> Based on this and other evidence, it has been proposed that, in laboratory animals, DA is associated with motivational aspects of drug taking.<sup>31</sup>

Recent APTD findings support a role for DA in the motivational aspects of human drug-taking behavior as well. For example, APTD has been shown to decrease alcohol consumption in social drinkers<sup>21</sup> and cigarette craving in nicotine-dependent smokers.<sup>17</sup> In both cases, APTD left various aspects of drug liking unaltered, suggesting that the diminished motivation for drug use was independent of the enjoyment of the drug effects. The effect of APTD on nicotine craving was prevented by L-DOPA.<sup>17</sup> Although preliminary, these findings raise the possibility that the

**Table**  
**Effects of APTD on Mood and Motivational States in Healthy Men and Women**<sup>5,11,16,17,19-23</sup>

Study	Motivation/Reinforcement	Mood
Leyton et al <sup>5</sup>	Increased levels of boredom	Increased depressed mood following the completion of a stressful task; no significant effect prior to challenge
Harmer et al <sup>11</sup>	Not tested	Decreased "feel good" scores; no significant effect on "depressed" scores
McTavish et al <sup>16</sup>	Not tested	Decreased "mind race" and "buzz" feelings following methamphetamine in healthy individuals; decreased manic symptoms in patients with bipolar disorder
Casey et al <sup>17</sup>	Decreased cigarette craving but not cigarette liking; craving effect was reversed by L-DOPA	No significant mood effects reported
McLean et al <sup>19</sup>	Increased apathy, decreased salience of rewarding cues in a decision-making task	Decreased "feel good" scores; increased bias for negative affect related stimuli.
Leyton et al <sup>20</sup>	Decreased <i>d</i> -amphetamine enhanced responding for rewarding cues; effect was reversed by L-DOPA	Decreased subjective effects of <i>d</i> -amphetamine; effect not reversed by L-DOPA
Leyton et al <sup>21</sup>	Decrease alcohol ingestion, but not alcohol liking	Not tested
McTavish et al <sup>22</sup>	Not tested	Decreased "mind race" effect of <i>d</i> -amphetamine; no effect was evident prior to amphetamine challenge
Coupland et al <sup>23</sup>	Not tested	No significant mood effects

APTD=acute phenylalanine/tyrosine depletion; L-DOPA=3,4-dihydroxy-L-phenylalanine.

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neurobiological substrates of drug wanting versus liking can be demarcated using the APTD method, and that DA is more closely related to the former.

### Mood

In addition to their motivational effects, catecholamines have also been hypothesized to be involved in the regulation of mood. This is primarily based on observations that drugs that enhance catecholamine function tend to elevate mood, drugs that inhibit catecholamines tend to lower mood, and abnormal peripheral markers of catecholamine function are evident in patients with affective disorders.<sup>3</sup> Although most evidence linking catecholamines to mood remains indirect, recent APTD studies support a role for catecholamines in the mediation of positive and negative affective states. In some studies,<sup>5,11,31</sup> though not in all studies,<sup>22,23</sup> APTD has been reported to produce mild mood-lowering effects in healthy individuals. In one study,<sup>19</sup> subjects reported feeling less “content” and displayed a greater negative word bias in a word-response task following the ingestion of the APTD mixture, while in a second study,<sup>11</sup> APTD significantly decreased ratings of “feeling good.”

Evidence suggests that effects of APTD on mood may be greater when there is increased demand on catecholamine function. In the one study<sup>5</sup> meant to explicitly assess this possibility, a depressogenic effect of APTD was seen following a stressful psychological challenge but not before it. Similarly, studies<sup>22</sup> suggest that APTD diminishes subjective effects of psychostimulant drugs without altering mood before drug administration.

The evidence that various “challenge” conditions might augment mood-lowering effects associated with APTD is consistent with the neurobiological data. Microdialysis studies in rodents<sup>8</sup> and PET studies in humans<sup>12,13</sup> indicated that APTD has greater effects on DA transmission relative to resting baseline, following amphetamine administration. These findings suggest that APTD may be particularly well suited for examining psychiatric disorders characterized by hyperactive catecholamine activity while leaving normal function unaltered.

### Bipolar Disorder

Indirect evidence has linked bipolar

disorder with abnormalities in catecholamine functioning. For example, peripheral markers for NE functioning are increased during mania<sup>34</sup> and have been shown to correlate with lithium-induced changes in mood.<sup>34</sup> In addition, several variations of genes that code for different DA receptors have been identified as potential markers for bipolar disorder<sup>35</sup> and medications with known D<sub>2</sub> receptor antagonist actions are efficacious in treating bipolar symptoms.<sup>35</sup>

A recent investigation examined the effect of APTD on manic symptoms in an inpatient group of bipolar patients being treated with DA D<sub>2</sub> medications.<sup>16</sup> In this study, APTD reduced manic symptoms by approximately 35%. Because APTD effects on DA and NE were not differentiated, it is not clear if the observed effect resulted from an augmentation of the medication’s D<sub>2</sub> effects or from a reduction in function at other DA or NE receptor subtypes. Although further work is required to delineate the precise mechanism of therapeutic action, these findings provide the first evidence that APTD can exert clinically significant effects in a psychiatric population.

### Therapeutic Potential of Catecholamine Depletion

Given the evidence that APTD can acutely reduce manic symptoms and drug craving, there has been interest in developing the method for longer term administration. The original method, though, is not appropriate for long-term use. APTD requires that patients follow a strict low-protein diet so that other sources of phenylalanine and tyrosine do not become available. Moreover, because APTD induces protein synthesis and this requires phenylalanine and tyrosine from the body’s remaining stores, repeated APTD administration over prolonged periods could result in malnutrition or tissue damage.

A recently developed variant of the APTD technique that is not believed to induce protein synthesis may be appropriate for long-term use.<sup>36</sup> It consists of an amino acid mixture containing three branched-chain amino acids (BCAAs)—leucine, isoleucine, and valine—which compete with phenylalanine and tyrosine for transport into the brain. Preliminary evidence

using this technique suggests that ingestion of a BCAA mixture may exert observable effects on catecholamine transmission. For example, BCAA administration has been demonstrated to produce cognitive and endocrine effects consistent with diminished DA function in healthy humans,<sup>36</sup> as well as to acutely reduce manic symptoms in patients with bipolar disorder by approximately 20%.<sup>37</sup> This latter effect, albeit weaker than that associated with APTD, demonstrates that BCAA mixtures can exert clinically significant effects, and they may have utility for the treatment of psychiatric disorders characterized by hyperactive catecholamine activity.<sup>16,37</sup>

### Conclusion

APTD appears to be a safe, effective, and well-tolerated method for rapidly decreasing catecholamine transmission and investigating their role in the regulation of various normal and abnormal behaviors. Preliminary APTD studies in healthy individuals support the role of catecholamines in motivational, reinforcement, and affective processes. Studies in nicotine-dependent smokers and bipolar patients suggest that APTD can decrease drug craving and manic symptoms. Although APTD does not appear to be suitable for long-term psychiatric treatment, a variation of the method does show some promise for extended therapeutic use. Potential applications of APTD and related methods include investigating the role of catecholamines in the pathogenesis and symptom expression of various psychiatric disorders, delineating the mechanisms of therapeutic drug action, augmenting treatment response in hyper-catecholamine disorders, and identifying individuals at risk. **PP**

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