Low Dose Alpha-Methyl-Para-Tyrosine (AMPT) in the Treatment of Dystonia and Dyskinesia

Ralph Ankenman, M.D.
Michael F. Salvatore, Ph.D.

AMPT (alpha-methyl-para-tyrosine) is an inhibitor of tyrosine hydroxylase, the rate-limiting enzyme in dopamine biosynthesis. In clinical settings, AMPT is approved to treat pheochromocytoma. Dystonias and dyskinesias seem to have their origin in inconsistent regulation of dopamine function in dopamine pathways. This paper presents case histories of the clinical efficacy of AMPT for treating certain individuals with neuroleptic-induced dystonia or dyskinesia. The authors propose that a special utility of AMPT in tardive disorders may be related to a downregulation of tyrosine hydroxylase activity that may be increased by neuroleptic-induced effects on tyrosine hydroxylase phosphorylation.

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Tyrosine hydroxylase is the rate-limiting enzyme of the biosynthesis of catecholamines. It converts l-tyrosine to l-dopa. The compound alpha-methyl-p-tyrosine (AMPT) competes with l-tyrosine at the tyrosine-binding site, causing inhibition of tyrosine hydroxylase. In 1965, Sjoerdsma et al.[1] reported the ability of AMPT to alter catacholamine synthesis in man. Engelman et al.[2] reported its use to lower catacholamine levels in 52 patients with pheochromocytoma. AMPT has been used extensively in human and animal research for its ability to deplete dopamine, and clinical trials have been reported in various disease states in which dysfunctional dopamine homeostasis is implicated. It has been used as a supplement to antipsychotics,[3] in movement disorders like tardive dyskinesia,[4,5] in Huntington's disease,[6] and for lowering cravings in substance abuse.[7] Nevertheless, AMPT has not acquired regular clinical use, though it is occasionally mentioned as a possible treatment in refractory dystonia or dyskinesia.[8]

Intracellular Dopamine

There is evidence of two functional pools of dopamine within the dopaminergic cell.[9] These pools, the cytosolic

Received August 17, 2005; accepted October 31, 2005. Dr. Ankenman is affiliated with the Department of Anatomy and Neurobiology, University of Kentucky, Lexington, Kentucky. Dr. Salvatore is affiliated with Madison County Hospital, London, Ohio. Address correspondence to Dr. Ankenman, 306 Whitney-Hendrickson Building, 800 Rose Street, Lexington, KY 40536; docank@newave.net (e-mail).

pool (or newly synthesized pool) and vesicular pool (stored pool) are often distinguished by their different response to the dopamine-depleting drugs.[10] The primary effect of AMPT is to limit the amount of newly synthesized dopamine formed in the cytosol by lowering the production of dopamine via direct inhibition of tyrosine hydroxylase. Reserpine and Tetrabenezine prevent the uptake of dopamine into vesicular stores, which ultimately results in a loss of cellular dopamine.[11]

The dosages of AMPT recommended for most clinical trials and the treatment of pheochromocytoma range from 1000 to 3000mg/day, which substantially reduce catacholamine biosynthesis (36% to 80%).[12] We propose that the clinical effect of low doses of AMPT is to modify neuroleptic-related increases in cytosolic dopamine by direct inhibition of tyrosine hydroxylase. By affecting the fluctuations that occur in dopamine production, AMPT provides a therapeutic benefit not available with the use of other dopaminergic medications.

Phosphorylation of Tyrosine Hydroxylase

Under physiological conditions, the activity of tyrosine hydroxylase is regulated by phosphorylation at Ser31 (Serine31) or Ser40.[13] Phosphorylated tyrosine hydroxylase has enhanced efficacy in dopamine synthesis. Various stimuli, including N-methyl-D-aspartic (NMDA) receptor stimulation,[14] nicotine,[15] and histamine,[16] have been shown to affect the activity of tyrosine hydroxylase through phosphorylation at these serine residues.[17] Antipsychotics such as thioridazine or clozapine increase tyrosine hydroxylase activity,[18] likely through increases of phosphorylation of tyrosine hydroxylase at Ser31 or Ser40 via dopamine-2 (D2) receptors.[19] These increases in tyrosine hydroxylase phosphorylation occur following administration in both naive animals[20] and in animals that have been chronically administered antipsychotics for 2 weeks.[19] Therefore, neuroleptic treatment has the potential to cause transient upregulation of dopamine levels which may be more than necessary for normal execution of motoric function and, as a result, cause dystonia or dyskinesia.

Case Studies Using Low-Dose AMPT

Since AMPT acts directly on tyrosine hydroxylase, and probably bypasses phosphorylation effects caused by antipsychotics, it is possible that low dose AMPT might have a special benefit in tardive dyskinesia. We report three cases in which the use of AMPT (at 1 gram per day or less) had efficacy in the treatment of movement disorders, which was superior to previous treatments.

Case 1. Constant Tremor and Intermittent Dystonia Secondary to Brain Trauma

We saw an adolescent woman 10 years after she sustained a brain injury at the age of seven. Her right arm presented a Parkinson-like tremor resulting from the injury. She also had episodic "attacks" of painful dystonia, during which she often gripped an object so tightly that it was nearly impossible to pry her hand loose. Occasionally, ego-alien hallucinations accompanied these episodes. Both symptoms occurred more often when she was anxious. The hallucinations had not responded to a regimen of olanzapine, 20mg/day, and botulinum toxin injections had been minimally helpful for the dystonia. The anticholinergic trihexyphenidyl helped the tremor but not the dystonia. Since the episodes of dystonia were linked with hallucinations, we presumed they resulted from excess dopaminergic activity, similar to tardive dystonia. A trial of low-dose pimozide did not improve the hallucinations or dystonia, but did worsen her tremor. She was then placed on a regimen of AMPT, 250mg/day. This quickly improved the hallucinations and the dystonia, but 500mg/day caused an increase of the tremor. The dystonia recurred when AMPT was temporarily stopped. She obtained maximal benefits on risperidone 0.5mg q.i.d., haloperidol, 0.125mg t.i.d., and AMPT 325 mg/day. Later she tolerated a downward titration of the antipsychotics. She had a mild dystonic reaction less than once a week. Her arm is reasonably useful despite the continued tremor. She remained stable for 3 years, then was transferred to local care.

Case 2. The Use of AMPT to Mask Acute Tardive Dystonia

A 25-year-old profoundly retarded woman had episodes of severe aggression over a 10-year period. She was hospitalized in a nonaffiliated psychiatric hospital where her neuroleptic dose was raised to haloperidol, 10mg, plus olanzapine, 20mg/day. After discharge, she demonstrated severe akathisia, which was relieved by titrating her off of the haloperidol. Three weeks later the olanzapine was rapidly replaced by quetiapine, 300mg/day, because of an elevated sodium level. Within 4 days she developed multiple symptoms of severe dystonia.

She lost her ability to walk, and her left elbow became fixed in a flexed position. She had swallowing and breathing problems when eating. She was admitted to the medical unit of an affiliated hospital for treatment of aspiration pneumonia. Increasing the antipsychotic dose caused increased dystonic rigidity. She was then placed on clozapine, 125mg/day, which stabilized her psychiatric condition, but dystonia continued in her limbs preventing normal daily function. The addition of AMPT, 250mg q.i.d., relieved her dystonia sufficiently to allow for appropriate care. The dystonia then began to resolve—allowing for titration of the AMPT to 250mg b.i.d. Her eating, walking, and muscle movements were nearly normal within 6 weeks. It is uncertain whether the dystonia resolved spontaneously, through the action of the clozapine, or by some action of the AMPT. However, it is evident that the dystonia was neutralized by the AMPT, making her physical care much easier.

Case 3. Relief of Symptoms of Long-Standing Tardive Dyskinesia Using a Very Low Dose of AMPT

A 40-year-old mildly retarded woman was seen over a 10-year period for psychiatric difficulties related to childhood abuse. She also had a long-standing history of tardive movements. Her first tardive dyskinesia symptoms occurred 4 months after she had received a neuroleptic for the first time and were described as eye blinking, mouth movements, and walking with an arched back. Originally she responded to this clinic's standard protocol for treating tardive dyskinesia with a neuroleptic and amantadine.[21] After 2 years of slow titration, she was off the neuroleptic and amantadine without symptoms of tardive dyskinesia. Later, we began a regimen of risperidone to relieve psychotic symptoms. She quickly developed tardive dyskinesia movements. This time, the combination of neuroleptic and amantadine provided no benefit. Treatment with clozapine also was ineffective. She was given a short trial of 1g of AMPT, which was discontinued because of pseudo-parkinsonian tremor. After years of waxing and waning symptoms, including excess eye blinking, erratic shoulder and arm movements, mouth movements, and swallowing difficulties, AMPT, 250mg three times a week, was added to her complex regimen of multiple antipsychotics, which had been only partially helpful. This markedly lowered her abnormal movements, and has allowed the antipsychotic dosage to be lowered more than 50%. She was stable for 3 years but recently increasing dysphagia required changes in her medication regime, which has caused a return of some limb dyskinesia.

Clinical Experience With Dopamine-Depleting Drugs

Reserpine, one of the early drugs which lowered dopamine activity, never attained wide clinical use because of significant side effects.[22] This clinic formerly used reserpine as an adjunctive to neuroleptics for treating the episodic psychotic symptoms commonly seen in the developmentally disabled population. Reserpine sometimes lowered the intensity and frequency of such psychotic reactions but also caused side effects of sedation, sluggishness, and depression. In the mid-1980s, AMPT was substituted for reserpine. Currently, 30 clinic outpatients are receiving AMPT, with only one receiving more than 1000mg/day. The majority had a long history of severe violence related to psychosis. The rest had various conditions including episodes of nonviolent psychosis, autistic impulsivity, violence related to nicotine craving, and movement disorders. Nearly all of these current patients have failed attempts to titrate down the AMPT.

Side Effects

Since the dose of AMPT is low, the side effects listed in the manufacturer's description, such as crystalluria, diarrhea, anxiety, and depression, have not been seen. All of the individuals who received AMPT at this clinic were also receiving antipsychotics, and a number of patients have demonstrated side effects, such as prolactin elevations and pseudo-Parkinson movement disorders. Since AMPT blocks dopamine synthesis, treatment of movement side effects requires restitution of dopamine using l-dopa or l-tyrosine. This clinic's protocol to treat movement side effects stops the AMPT and gives four doses of clinic-supplied l-tyrosine (1000mg every 12 hours). Symptoms generally clear quickly after the first dose of l-tyrosine. Use of the combination of AMPT and reserpine in eight patients demonstrated no increased benefit but did produce increased movement side effects, including two cases of neuroleptic malignant syndrome.

Effect of Chronic Antipsychotics on Tyrosine Hydroxylase Function

The delayed motoric side effects of neuroleptics are classified as tardive disorders. Tardive dyskinesia and tardive dystonia are observed in roughly 25% of patients treated with neuroleptics.[23] The basal ganglia plays a primary role in motoric function, and within it, the nigrostriatal dopamine pathway has a major part in volitional aspects of the initiation of movement. It is thought that imbalance of D2 receptor expression in the basal ganglia is induced by chronic neuroleptics.[23] Neuroleptic-induced increases in tyrosine hydroxylase phosphorylation were first described in both the nigrostriatal and mesolimbic systems in vivo by Salvatore et al.[20] This study also showed that haloperidol elevated phosphorylation at Ser19 in the striatum, a site recently shown to affect the ability of Ser40 to phosphorylate.[24] Because phosphorylation of tyrosine hydroxylase at Ser31 or Ser40 can increase dopamine biosynthesis, the neuroleptic-induced increases in Ser31 or Ser40 would be expected to elevate levels of dopamine in dopamine pathways. Recently, it has been shown that D2 receptors play a role in the neuroleptic-induced increase in tyrosine hydroxylase phosphorylation at Ser31 and Ser40 in the striatum.[25] Because tyrosine hydroxylase phosphorylation increases from a single administration of neuroleptics either in naïve animals or in animals undergoing chronic neuroleptic administration, a hyperdopaminergic tone in the basal ganglia could be the end result of the use of neuroleptics and may predispose certain individuals to tardive dyskinesia or tardive dystonia. The use of AMPT would bypass the increase in phosphorylation caused by neuroleptics, and perhaps restore a functionally normal level of dopamine.

The Unique Pharmacology of AMPT

Although none of the reported cases is completely stable, the use of AMPT did provide some therapeutic control of neuroleptic-induced motor dysfunctions. The apparent capacity of low-dose AMPT to provide therapeutic benefits suggests that dopamine activity can be stabilized by manipulating the activity of tyrosine hydroxylase and its effect on the cytosolic dopamine storage pool. The effect of antipsychotic use on the activity of tyrosine hydroxylase may be a contributor to the phenomenon of tardive movement disorders. Therapy with AMPT seems to offer a way to offset the presumed increases in dopamine function that occur with the use of antipsychotics which contribute to the tardive movement disorder.

References

1. Sjoerdsma A, Engelman K, Spector S, et al: Inhibition of catacholamine synthesis in man with alpha-methyl-tyrosine, an inhibitor of tyrosine hydroxylase. Lancet 1965; 286:1092–1094
2. Engleman K, Horwitz D, Jequier E, et al: Biochemical and pharmacological effects of A-methyltryosine in man. J Clin Invest 1968; 47:577–594
3. Walinder J, Skott A, Carlsson A, et al: Potentiation by metyrosine of thioridazine effects in chronic schizophrenics: a long-term trial using double-blind crossover technique. Arch Gen Psych 1976; 33:501–505
4. Fahn S: Treatment of tardive dyskinesia: use of dopamine-depleting agents. Clin Neuropharmacol 1983; 6:151–158
5. Lang AE, Masden CD: Alpha methylparatyrosine and tetrabenazine in movement disorders. Clin Neuropharmacol 1982; 5:375–387
6. Burke RE, Fahn S, Mayeaux R, et al: Neuroleptic malignant syndrome caused by dopamine-depleting drugs in a patient with Huntington's disease. Neurology 1981; 31:1022–1025
7. Pozuels J: Suppression of craving and withdrawal in humans addicted to narcotics or amphetamines by administration of alpha-methyl-para-tyrosine (AMPT) and 5-butylpicolinic acid (fusaric acid) treatment of narcotic and amphetamine addiction in humans: preliminary report. Cleve Clin Q 1976; 43:89–94
8. Adler CH: Strategies for controlling dystonia: overviews of therapies that may alleviate symptoms. Postgrad Med 2000; 108:151–160
9. Yavich L: Two simultaneously working storage pools of dopamine in mouse caudate and nucleus accumbens. Br J Pharmacol 1996; 119:869–876
10. Feldman RS, Meyer JS, Quenzer LF: Catecholamines, in Principles of Neuropsychopharmacology. Sunderland, Mass, Sinauer Associates, 1997, pp 277–344
11. Kannari K, Tanaka H, Maeda T, et al: Reserpine pretreatment prevents increases in extracellular striatal dopamine following l-dopa administration in rats with nigrostriatal denervation. J Neurochem 2000; 74:263–269
12. Demser (AMPT), in Physicians Desk Reference. Montdale NJ, Thompson PDR, 2005, p 2036
13. Salvatore MF, Waymire JC, Haycock JW: Depolarization-stimulated catacholamine biosynthesis: involvement of protein kinases and tyrosine hydroxylase phosphorylation sites in situ. J Neurochem 2001; 79:349–360
14. Lindgren N, Xu ZQ, Lindskog M, et al: Regulation of tyrosine hydroxylase activity and phosphorylation at Ser19 and Ser40 via activation of glutamate NMDA receptors in rat striatum. J Neurochem 2000; 74:2470–2477
15. Chalazonitis A, Rice PJ, Zigmond RE: Increased ganglionic tyrosine hydroxylase and dopamine-beta-hydroxylase activities following preganglionic nerve stimulation: role of nicotine receptors. J Pharmacol Exp Ther 1980; 213:139–134
16. Oishi R, Shishido S, Yamori M, et al: Comparison of the effects of eleven histamine H1-receptor antagonists on monoamine

turnover in the mouse brain. Naunyn Schmiedebergs Arch Pharmacol 1994; 349:140–144
17. Haycock JW: Multiple signaling pathways in bovine chromaffin cells regulate tyrosine hydroxylase phosphorylation at Ser19, Ser31, and Ser40. Neurochem Res 1993; 18:15–26
18. Zivkovic B, Guidotti A, Revuelta A, et al: Effect of thioridazine, clozapine, and other antipsychotics on the kinetic state of tyrosine hydroxylase and on the turnover rate of dopamine in the striatum and nucleus accumbens. J Pharmacol Exp Ther 1975; 194:37–46
19. Hakannson K, Pozzi L, Usiello A, et al: Regulation of striatal tyrosine hydroxylase phosphorylation by acute and chronic haloperidol. Eur J Neurosci 2004; 20:1108–1112
20. Salvatore MF, Garcia-Espana A, Goldstein M, et al: Stoichiometry of tyrosine hydroxylase phosphorylation in the nigrostriatal and mesolimbic system in vivo: effects of acute haloperidol and related compounds. J Neurochem 2000; 75:225–232
21. Ankenman R: The combination of amantadine and neuroleptics plus time may cure tardive dyskinesia. J Neuropsychiatry 1989; 1:96–97
22. Lopez-Munoz F, Bhatara VS, Alamo C, et al: Historical approach to reserpine discovery and its introduction in psychiatry. Actas Esp Psiquiatr 2004; 32:387–395
23. Goetz CG, Horn S: Tardive dyskinesia, in Movement Disorders: Neurologic Principles and Practice. Edited by Watts RL, Koller WC. New York, McGraw-Hill Medical Publishing, 2004, pp 629–637
24. Bobrovskaya L, Dunkley PR, Dickson PW: Phosphorylation of Ser19 increases both Ser40 phosphorylation and enzyme activity of tyrosine hydroxylase in intact cells. J Neurochem 2004; 90: 857–864
25. Lindgren N, Xu ZQ, Herrera-Marschitz M, et al: Dopamine D2 receptors regulate tyrosine hydroxylase activity and phosphorylation at Ser 40 in rat striatum. Eur J Neurosci 2001; 13:773–780