

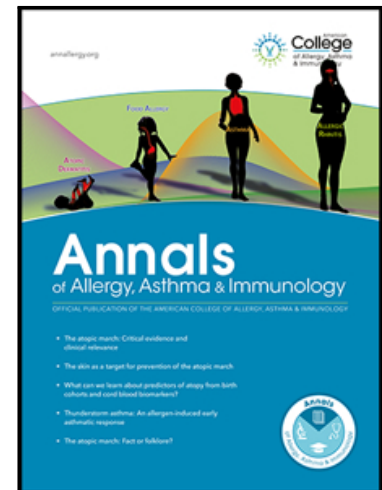
How Good Are Mast Cell Mediators?

Catherine R Weiler MD, PhD

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How Good Are Mast Cell Mediators?

Catherine R Weiler, MD, PhD

200 First St SW

Mayo Clinic, Division of Allergy

Rochester, MN 55905

Phone: 507-284-3783

Fax: 507-284-0902

Weiler.catherine@mayo.edu

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Abbreviations:

BST basal serum tryptase

H α T hereditary alpha tryptasemia

MC mast cell

SM systemic mastocytosis

Mast cells (MCs) are an integral part of the immune system. They play a pivotal role in several allergic and other immune responses. MCs store several mediators in their granules and synthesize new mediators which facilitate their function. The levels of some of those mediators and/or their metabolites are used for the diagnosis of MC activation and MC disorders.¹

However, recent data regarding some of those mediators need to be addressed and incorporated into the diagnostic criteria of MC activation and disorders.^{2,3}

The mediator, most commonly, used for the diagnosis of MC activation and MC disorders is the serine protease tryptase. MCs are almost exclusively the source of all serum tryptase in its two secreted isoforms α/β . Basophils produce 1% of measured serum tryptase. The only other cellular sources of tryptase are immature myeloid neoplastic cells. Because of its unique production by MCs, tryptase has been used as an MC marker. An increase in serum tryptase level above baseline is used as a marker of MC activation. An MC activation event is diagnosed when serum tryptase level increases by 20% + 2 ng/ml within a 1 to 4-hour period after the onset of a clinical crisis.¹ Furthermore, elevated basal serum tryptase (BST) level is one of the diagnostic criteria of systemic mastocytosis (SM). BST levels below 11.4 ng/ml are considered normal. A BST level above 20 ng/ml is a minor diagnostic criterium of SM.¹

Tryptase levels, however, need to be used with caution. BST levels can be increased in several other clinical conditions.^{1,4} A recently described clinical syndrome in which BST is elevated is hereditary alpha tryptasemia (H α T). H α T is an autosomal dominant genetic trait caused by increased germline copy numbers of the TPSAB1 gene. The two genes that encode secreted tryptase are TPSB2 and TPSAB1. While TPSB2 exclusively encodes β -tryptase, TPSAB1 can encode either α - or β -tryptase. The normal ratios of α - to β - tryptase can be either 0:4, 1:3, or 2:2. Because patients with H α T have an increase in the copy number of the α -encoding germline

TPSAB1 alleles, the $\alpha:\beta$ ratio is altered with higher expression levels of the α -tryptase isoforms. The $\alpha:\beta$ tryptase ratios in H α T are dependent on the TPSAB1 copy number. The $\alpha:\beta$ ratio can range from 2:3, 3:2 to higher α copy numbers. This increase in α -tryptase results in elevated measured BST levels, in the presence or absence of MC activation and MC disorders. The higher the TPSAB1 copy number, the higher the BST level. The level of BST in patients with H α T can range from 8 to >40 ng/ml.²

In a recent study, most patients with H α T did not have associated clinical phenotypes⁵, more studies are needed for further evaluation. Those who are symptomatic present with a variable number of seemingly unrelated symptoms. Some of the presenting symptoms include flushing, pruritus, vibratory urticaria, chronic pain, gastrointestinal symptoms, dysautonomia, joint hypermobility, postural orthostatic tachycardia syndrome, Ehlers-Danlos-like syndrome and neuropsychiatric symptoms.² They also have a high incidence of allergic disorders including anaphylaxis, especially to hymenoptera venom.³ It is worth noting that the severity of the symptoms directly correlates with the TPSAB1 copy number and BST levels.¹

The relation of H α T to MC activation needs to be evaluated. Data regarding the fluctuation in BST in patients with H α T are needed. The question of whether fluctuations of BST are equivalent to the presumed MC activation level changes must be addressed. H α T has been reported to affect 4-6% of the general population. Preliminary studies did not show an increase in SM cases in patients with H α T. However, about 17% of patients with SM have H α T.³ This suggests that H α T might play a pathophysiologic role in the development of SM, likely in concert with other cellular events. The use of BST levels as a diagnostic criterium of SM needs to be revisited. The addition of genetic testing for H α T could potentially be incorporated in the diagnostic criteria for SM. Alternatively, tryptase can be excluded from the diagnostic criteria

altogether. More studies are clearly needed to evaluate H α T and its relationship to MC activation and disorders.

Another validated MC mediator, used in clinical practice, is the urinary histamine metabolite N-methylhistamine. The urinary prostaglandin metabolites, 11 β -prostaglandin F 2α or 2,3-dinor-11 β -prostaglandin F 2α and the urinary leukotriene C metabolite, leukotriene E 4 are also validated mediators. Past testing of those mediators required collecting 24-hour urine samples, which limited their use. More recent available testing utilizes spot urine samples. One advantage of using the urinary metabolites as markers of MC activation and MC disorders, is the avoidance of invasive testing. Furthermore, the timeliness in sample collection is critical. Patients are usually provided with the urine collection kit at their home, which can be mailed to the lab. The disadvantage to using the urinary metabolites, is the limited availability of testing centers. Another disadvantage is the redundancy of cellular sources of those metabolites. Basophils generate histamine and eosinophils generate leukotrienes. Measurement of the levels of those urinary mediators has not been included in any of the consensus diagnostic criteria for MC activation or MC disorders.¹ Furthermore, no data is available about the urinary mediator levels in patients with H α T. The urinary breakdown products of mast cell mediators need to be studied further. Other products, such as chromogranin, are invalidated and do not relate to MC conditions.¹

It is time to look for and evaluate other MC mediator levels. This is an open field needed for the identification of new markers for the clinical evaluation of MC conditions. As the field of allergy and immunology continues to evolve, with new findings, so too must our clinical and laboratory practice. We are currently at a crossroad in the field of MC mediators. The current MC mediators are helpful but not good enough outside a comprehensive medical evaluation.

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