

This document refers explicitly to the effect of medications, specific clinical disorders and acute stressors on the biochemical interpretation of metadrenalines. Consider this when investigating a patient for phaeochromocytoma and paraganglioma.

Agent	Example	Mechanism	Plasma and Urine metadrenalines		
			NMA	MA	3-MT
Stimulants	Nicotine	Activation of nicotinic cholinergic receptors. Increased adrenal secretion of adrenaline	↑	↑	
	Caffeine	Mobilisation of intracellular calcium stores. Increased adrenal secretion of adrenaline			
Sympathomimetics	Amphetamine, methamphetamine	Increased released of monoamines from sympathetic nerves Inhibition of monoamine oxidase Blockage of neuronal cell membrane transporters	↑	↑	
	Ephedrine, pseudoephedrine	Activation of α - and β -adrenergic receptors Inhibit noradrenaline reuptake Inhibits function of vesicular monoamine function	↑	↑	
Noradrenaline receptor uptake blockers	Tricyclic antidepressants (e.g. Amitriptyline, clomipramine, desulepin)	Blockage of neuronal cell noradrenaline membrane transporters	↑↑		
	Venlafaxine, duloxetine	Blockage of neuronal cell noradrenaline membrane transporters			
	Cocaine	Centrally mediated sympathoinhibition	↑↑	↑	
Selective serotonin reuptake inhibitors	Citalopram, fluoxetine, sertraline	Inhibition of neuronal uptake of noradrenaline	↑↑		
α -adrenoreceptor blockers	Phenoxybenzamine, mirtazapine	Antagonism of α_2 -adrenoreceptors and sympathetic neurones	↑↑		
	Doxazosin	Antagonism of α -adrenoreceptors	[↑]		
β -adrenoreceptor blockers	Atenolol, labetalol, propranolol	Antagonism of β -adrenoreceptors		↑	
Monoamine oxidase inhibitors	Isocarboxazid, phenelzine, moclobamide	Blockade of deamination of O-methylated catecholamine metabolites	↑↑	↑↑	
Atypical anti-psychotics	Quetiapine, clozapine	Inhibition of dopaminergic, adrenergic and serotonergic receptors	↑		
	Risperidone	Antagonism of α_2 adrenoreceptors	↑		
DOPA related	L-DOPA, methyl-dopa	Metabolised by enzymes that also convert catecholamines			↑↑↑

Calcium channel blockers	Amlodipine, diltiazem	Activation of sympathetic nervous system	↑	↑	
Diet related*	Banana, pineapple, shelled walnuts, potatoes, tomatoes and beans	Increased intake of biogenic amines	↑		↑↑

Table 1. Potential pharmacological effects of prescribed and recreational drugs, and dietary agents on plasma and urine metadrenalines. MA – metadrenaline; MAO – monoamine oxidase; NMA – normetadrenaline; 3-MT – 3-methoxytyramine. **NOTE:** With the exception of phenoxybenzamine, **anti-hypertensives are not considered to cause appreciable false-positive test results for plasma and urine metadrenalines.** *If suspected diet related increases in metadrenalines are observed suggest overnight fasting for plasma free metadrenalines and dietary restrictions for total urinary fractionated metadrenalines.

It is generally not necessary to modify medication prior to plasma or urine metadrenalines testing. However, the medications in Table 1, where possible should be taken into consideration if positive results are obtained.

NOTE: If false positive results are suspected, suggest repeat sampling under idealised conditions. This includes, collecting plasma sample in a supine position after an overnight fast and at least 30 minutes in a recumbent position. Interfering medications should be withdrawn for at least two weeks if it is safe to do so, and with dietary modifications as required. Plasma samples should be sent to the laboratory on ice for immediate separation and freezing.

In addition to pharmacological effects on the concentration of plasma and urine metadrenalines also consider the impact of clinical disorders (Table 2) and acute physiological stressors (Table 3) which have the potential to cause significant elevations in metadrenalines

Condition	NMA	MA
Ischaemic heart disease	↑↑	↑
Cyanotic congenital heart failure	↑	
Acute intracerebral haemorrhage	↑↑	↑
Pseudo-pheochromocytoma		↑
Panic disorder/Anxiety	↑	↑↑
Pain		↑
Sleep apnoea syndrome	↑	
Renal failure	↑	
Acrodynia	↑↑	↑
Factitious catecholamine administration	↑	↑

Table 2. Clinical disorders with the potential to cause false-positive test results of metadrenalines in plasma or urine. MA – metadrenaline; NMA – normetadrenaline.

Acute daily stressor	Precaution
Vigorous exercise	Avoided during 24 h urine collection and for several hours before blood sampling
Seated or upright posture during sampling	Blood should be drawn after at least 20 mins of supine rested
Cold environment	Blood should be drawn after sufficient time to acclimate to warm inside temperatures
Acute emotional stress during venipuncture	For children or adult patients with needle phobia use indwelling canula or suggest 24 h urine collection
Stressful working day	Avoid 24 h urine collection during stressful working days

Table 3. Acute stressors associated with false-positive metadrenaline test results.

References

1. Brannan EH, et al. Elemental mercury poisoning presenting as hypertension in a young child *Pediatr Emerg Care*. 2012;28(8):812-814.
2. Carlson JT, et al. Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. *Chest* 1993;103(6):1763-1768.
3. Chidakel AR, et al. Utility of plasma free metanephrines in diagnosis of factitious pheochromocytoma. *Endocr Pract* 2006;12(5):568-571.
4. Eisenhofer G et al. Biochemical Assessment of Pheochromocytoma and Paraganglioma. *Endocrine Reviews* 2023;00:1–48.
5. Eisenhofer G, et al. Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. *J Clin Endocrinol Metab* 2003;88:2656-66.
6. Eisenhofer G, et al. Levodopa therapy in Parkinson's disease: influence on liquid chromatographic tandem mass spectrometric-based measurements of plasma and urinary normetanephrine, metanephrine and methoxytyramine. *Ann Clin Biochem* 2014;51:38–46.
7. Eisenhofer G, et al. Plasma metadrenalines: do they provide useful information about sympatho-adrenal function and catecholamine metabolism? *Clin Sci (Lond)* 1995;88(5): 533-542.
8. Eisenhofer G, et al. Plasma metanephrines in renal failure. *Kidney Int* 2005;67(2):668-677.
9. Hamann GF, et al. Pattern of elevation of urine catecholamines in intracerebral haemorrhage. *Acta Neurochir (Wien)* 1995;132(1–3):42-47.
10. Hasking GJ, et al. Norepinephrine spillover to plasma in patients with congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. *Circulation* 1986;73(4):615-621.
11. Jazdarehee A, et al. Pseudo-pheochromocytoma due to obstructive sleep apnea: a case report. *Endocrinol Diabetes Metab Case Rep* 2022;2022: 21-0100.
12. Jensterle M, et al. Comparison of plasma metanephrines in patients with cyanotic and acyanotic congenital heart disease. *Endocrine* 2022;78(3): 580-586.
13. Keiser HR. Surreptitious self-administration of epinephrine resulting in 'pheochromocytoma' *JAMA*. 1991;266(11):1553-1555
14. Neary NM, et al. Drugs and pheochromocytoma--don't be fooled by every elevated metanephrine. *New Eng J Med* 2011;364:2268-70.
15. Peitzsch M, et al. Interference from 3-O-methyldopa with ultra-high performance LC-MS/MS measurements of plasma metanephrines: chromatographic separation remains important. *Clin Chem* 2015;61:993–996.
16. Robertson D, et al. Comparative assessment of stimuli that release neuronal and adrenomedullary catecholamines in man. *Circulation* 1979;59(4):637-643.
17. Schürfeld R, et al. False-positive results for pheochromocytoma associated with norepinephrine reuptake blockade. *Endocrine-Related Cancer* 2024;31:e230063.
18. Sharabi Y, et al. Sympathoadrenal function in patients with paroxysmal hypertension: pseudopheochromocytoma. *J Hypertens* 2007;25(11):2286-2295.
19. Wilkinson DJ, et al. Sympathetic activity in patients with panic disorder at rest, under laboratory mental stress, and during panic attacks. *Arch Gen Psychiatry* 1998;55(6):511-520.