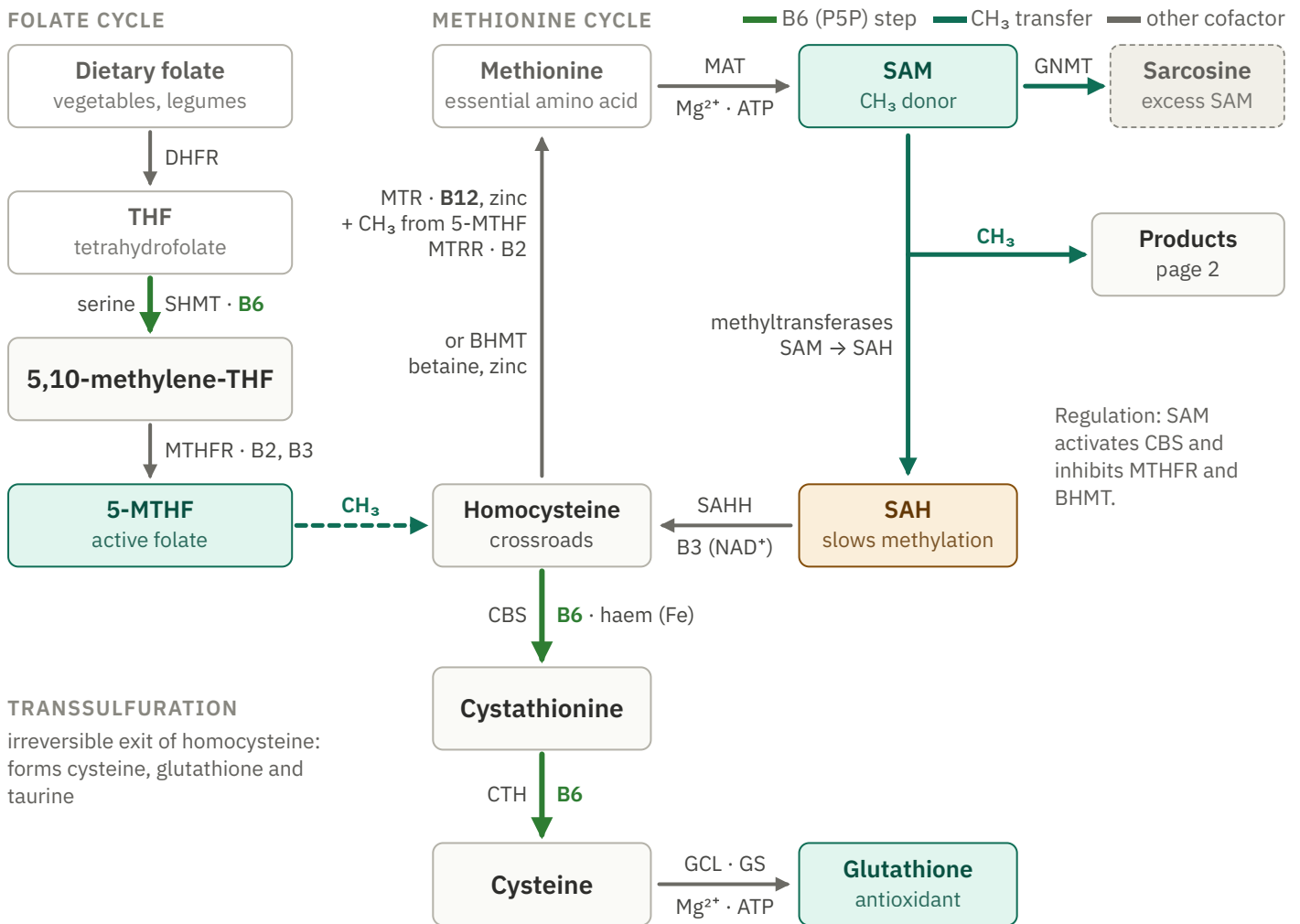


Methylation: how vitamins power it

Methylation is the transfer of a small $-CH_3$ group from one molecule to another. It takes place in every cell, and its only donor is SAM. To keep the cycle running, enzymes need vitamins and minerals as their tools.



Vitamins and minerals as tools of the cycle

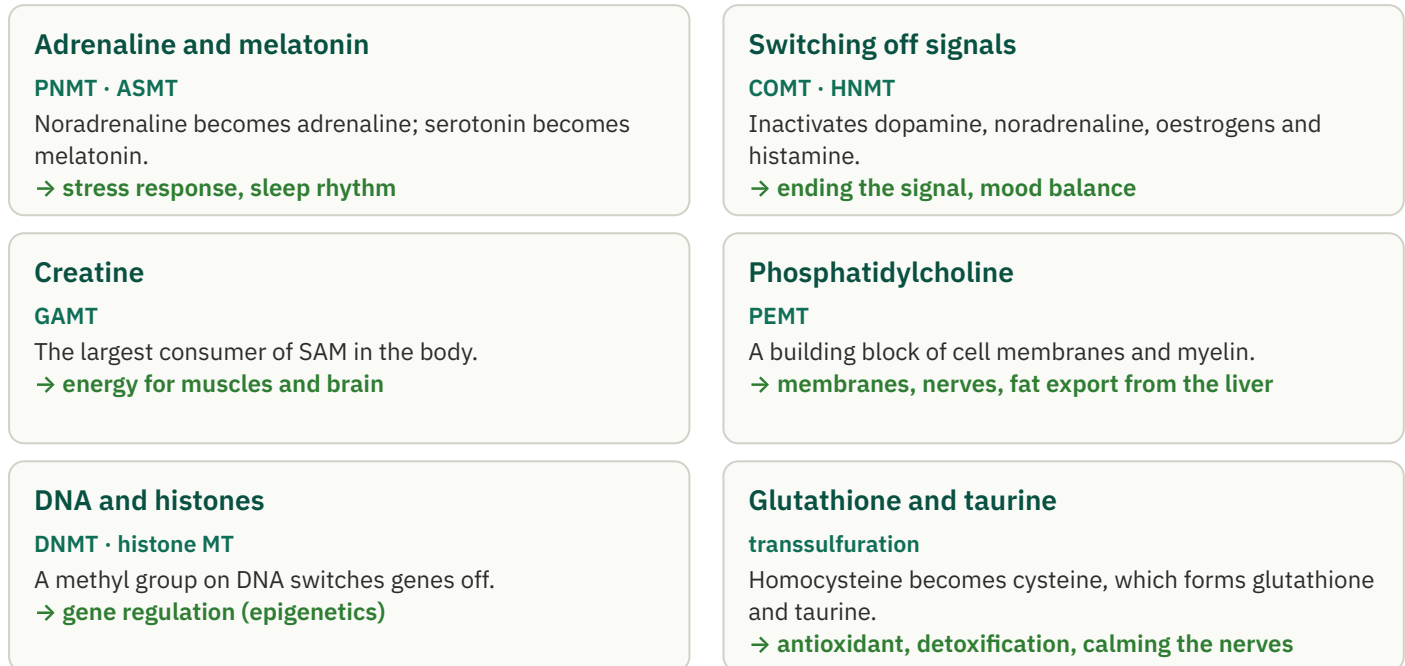
Vitamin / mineral	Enzyme	What it does in the cycle
Magnesium (+ ATP, potassium)	MAT	makes SAM from methionine
Vitamin B12	MTR – methionine synthase	recycles homocysteine back to methionine
Folate (5-MTHF)	MTR	supplies the CH ₃ group for recycling homocysteine
Vitamin B2 (FAD, FMN)	MTHFR, MTRR	forms active folate and keeps B12 active
Vitamin B3 (NAD ⁺ , NADPH)	SAHH, MTHFR	removes SAH, helps form 5-MTHF
Vitamin B6 (P5P)	SHMT, CBS, CTH	feeds CH ₃ into the folate cycle, removes homocysteine
Zinc	BHMT, MTR	drives the backup recycling via betaine
Betaine (TMG), choline	BHMT	backup CH ₃ donor, especially in folate deficiency
Iron	CBS (haem), SHMT	removing homocysteine, folate cycle

Key point: methylation keeps running as long as SAH and homocysteine are continuously removed. The liver keeps SAM levels stable, so the SAM/SAH ratio changes mainly when SAH accumulates.

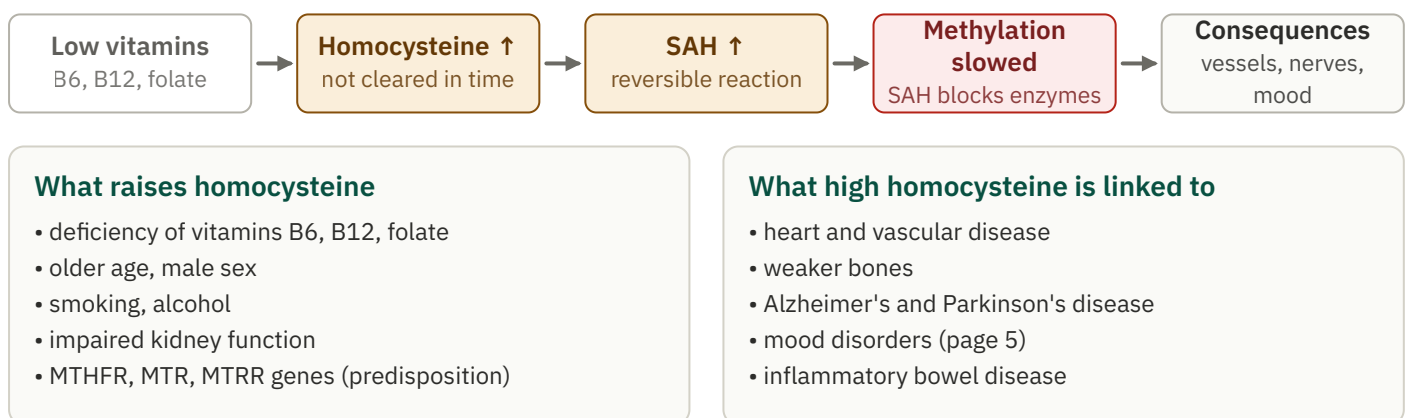
What methylation makes and why it matters

Every methyl group from SAM does a job: it makes hormones, switches off signals, builds membranes and controls genes. The by-products are SAH and homocysteine, which the body must remove continuously.

FIG. 1 – SAM IS THE ONLY CH₃ DONOR FOR MORE THAN 100 REACTIONS

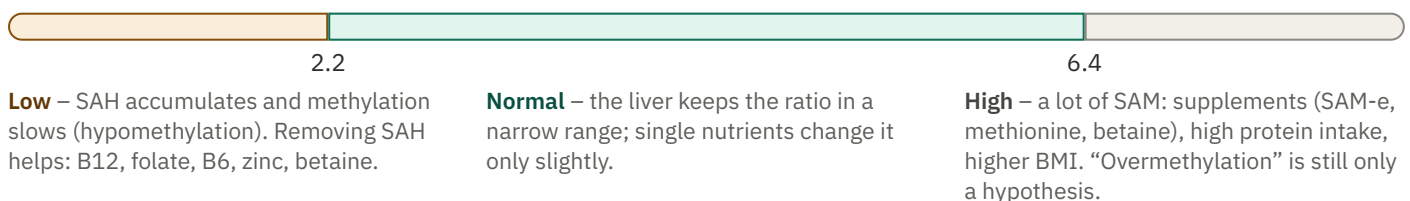


When methylation falls behind



Methylation index: the SAM/SAH ratio

The SAM/SAH ratio shows how much “fuel” (SAM) a cell has relative to the “brake” (SAH). A healthy ratio is not 1 : 1; there should be considerably more SAM. Genova gives a plasma reference range of **2.2–6.4**.

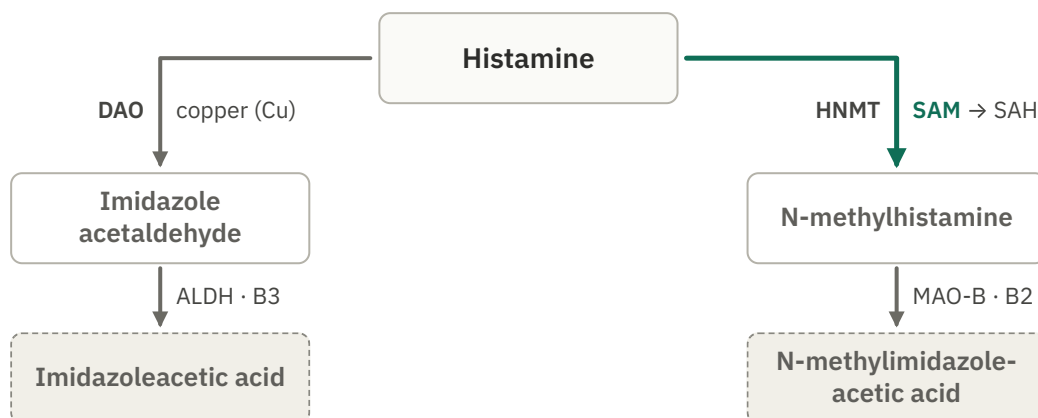


Histamine and methylation

The body breaks down histamine by two routes. The methylation cycle affects only one of them: the enzyme HNMT, which needs SAM to work.

FIG. 1 – TWO ROUTES OF HISTAMINE BREAKDOWN

— methylation (SAM → SAH) — other cofactor



Route 1: DAO – in the gut

- breaks down dietary histamine, outside cells
- the enzyme contains copper
- does not depend on SAM or methylation

Route 2: HNMT – inside cells

- brain, liver, kidneys, lungs, gut
- needs SAM and is slowed by accumulating SAH
- the only route affected by the methylation cycle

HNMT is supported by: enough SAM (methionine, magnesium, ATP) and continuous removal of SAH and homocysteine (B12, folate, B6, zinc, betaine, B3).

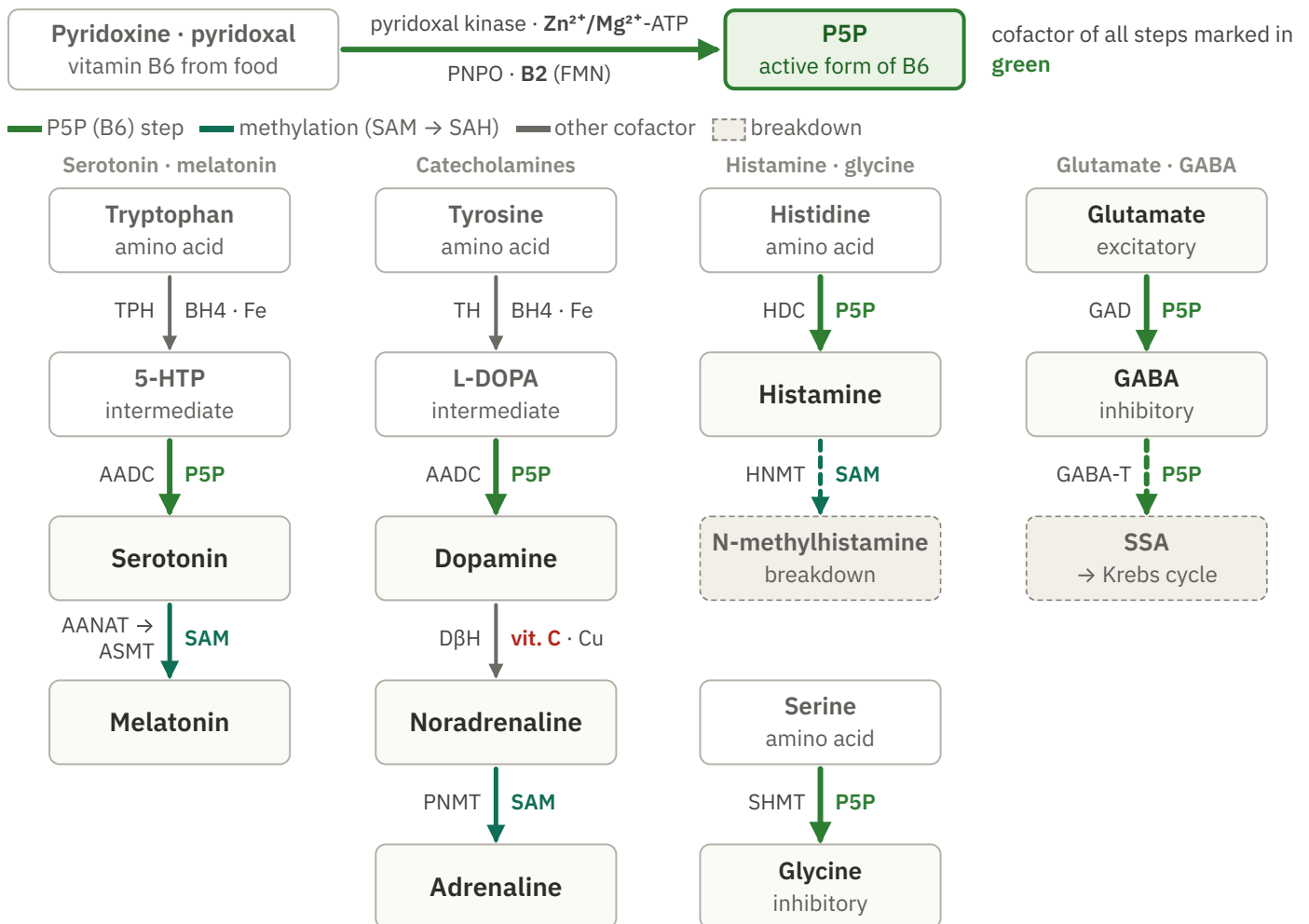
How to read this

- Cofactors enable normal enzyme function; they do not speed enzymes up beyond normal.
- The SAM/SAH ratio is tightly regulated; supplements shift it mainly by removing SAH (page 2).
- To assess: whole-blood histamine, serum DAO activity, homocysteine; SAM, SAH and their ratio in a methylation panel.

Neurotransmitters and vitamin B6

Vitamin B6 in its active form P5P is a cofactor of the enzymes that make serotonin, dopamine, histamine, GABA and glycine from amino acids. Methylation (SAM) acts only on the finished neurotransmitters.

FIG. 1 – B6 ACTIVATION AND NEUROTRANSMITTER SYNTHESIS



Methyltransferases: where SAM acts on neurotransmitters

Enzyme	Reaction	Cofactor	Significance
ASMT	N-acetylserotonin → melatonin	SAM	sleep; made in the pineal gland
PNMT	noradrenaline → adrenaline	SAM	stress response; adrenal medulla
COMT	dopamine, noradrenaline, adrenaline, oestrogens → methoxy derivatives	SAM, Mg ²⁺	breakdown; the COMT V158M variant is linked to anxiety
HNMT	histamine → N-methylhistamine	SAM	histamine breakdown in the brain (page 3)

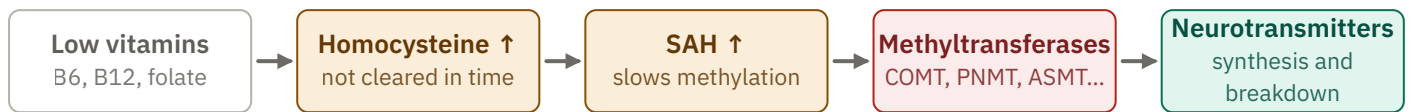
Important connections

- The rate of serotonin and dopamine synthesis is set by TPH and TH (BH4, iron), not by P5P.
- P5P from a supplement is first converted to pyridoxal in the gut; in cells, pyridoxal kinase (Zn, Mg) reactivates it.
- Melatonin is made in two steps: AANAT acetylates serotonin, and only then ASMT methylates it using SAM.
- Besides methylation, serotonin, dopamine and noradrenaline are broken down mainly by MAO (cofactor FAD from B2).

Methylation, anxiety and depression

Research links mood disorders to methylation mainly through homocysteine and SAH. Nutrition can support the methylation cycle, but it does not replace treatment of anxiety and depression.

FIG. 1 – HOW METHYLATION CAN AFFECT MOOD



What research says

Homocysteine and mood

High homocysteine is linked to mood disorders and to neurodegeneration. The mechanism is multiple: SAH slows methyltransferases and homocysteine also acts on nerves directly. Folate, B12 and SAM have been shown to lower it.

SAM-e in depression

In studies SAM-e was effective in depression, comparable to tricyclic antidepressants, and well tolerated. In bipolar disorder, however, it can trigger mania, so use it only after agreement with a doctor.

Vitamin B6 (P5P)

It is a cofactor in making serotonin, dopamine and GABA (page 4) and removes homocysteine. Long-term high doses can damage nerves; the EFSA upper limit is 12 mg per day.

Genes as a predisposition

MTHFR C677T has been linked to depression, MTRR A66G to mood disorders and COMT V158M to anxiety and panic disorder. A gene variant does not mean disease, only greater sensitivity to vitamin deficiency.

Glycine, sarcosine and taurine

They act on NMDA and other receptors and dampen nerve excitability. They are being studied as add-on treatments but are not yet standard.

Tests worth doing

Test	What it shows	Note
Homocysteine (plasma)	whether the body keeps up with clearing homocysteine	widely available; the best first step
Vitamin B12 and folate	stores for recycling homocysteine	if B12 is borderline, also active B12 (holoTC)
SAM, SAH, SAM/SAH index	the cell's methylation capacity	specialised panel; Genova reference 2.2–6.4
MTHFR, MTRR, COMT genes	predisposition	not a diagnosis; assess together with blood tests

Authorised claims (Regulation (EU) 432/2012)

Vitamin B6, vitamin B12 and folate contribute to normal homocysteine metabolism. Vitamin B6, vitamin B12, folate, niacin, vitamin C and magnesium contribute to normal psychological function.

When to see a doctor

Anxiety and depression are illnesses that belong in the hands of a doctor or psychologist. Nutrition and supplements can support treatment but do not replace it. Do not stop antidepressants or other treatment without your doctor. If you have thoughts of self-harm, seek help immediately (doctor, emergency number 112 or your local emergency number).