Concise analysis of the assimilation of all forms of vitamin B12 by the human body

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Vitamin B12 is an essential vitamin the human body requires for its important role in cellular metabolism. Cyanocobalamin (CNCbl) and hydroxocobalamin (OHCbl) are frequently used to treat vitamin B12 deficiencies, but in recent years adenosylcobalamin (AdoCbl) and methylcobalamin (MeCbl) have emerged as "superior" supplements of Cbl. However, this notion is incorrect as all forms of supplemental (and food-derived) vitamin B12 are processed similarly by human cells.

Vitamin B12, also known as cobalamin (Cbl), is an essential micronutrient required by all cells in the human body. Cbl occurs in four near-identical forms: Hydroxylcobalamin (OHCbl), methylcobalamin (MeCbl), adenosylcobalamin (AdoCbl) and cyanocobalamin (CNCbl). These forms all have a similar chemical structure, except for their upper ligand (see Figure 1 and Table 1). OHCbl, MeCbl and AdoCbl are present in animal-sourced foods, whereas CNCbl is a synthetic form. Once ingested, the protein haptocorrin binds to the B12 form to protect it from the hydrochloric acid found in the stomach and presents it to the Gastric Intrinsic Factor (GIF), which encodes the B12 form and presents it to the blood stream, where it can be absorbed by a cell.

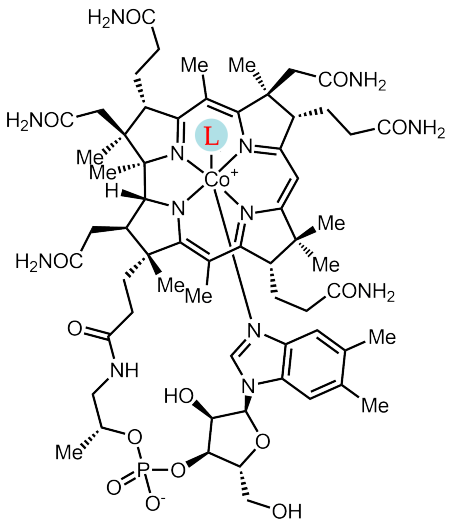

Figure 1: The chemical structures of vitamin B12. L(igand) can have any of the structures listed in Table 1. Edited picture from Wikipedia [Wikipedia, 2020]

L(igand)	**cobalamin form**
H_2O	Hydroxylcobalamin (OHCbl)
CH_3	Methylcobalamin (MeCbl)
5'-deoxyadenosyl	Adenosylcobalamin (AdoCbl)
CN	Cyanocobalamin (CNCbl)

Table 1: The upper ligand and associated form of vitamin B12.

AdoCbl and MeCbl both act as coenzymes for several biologial reactions in the human cell, which is why they are the active forms of vitamin B12. OHCbl and CNCbl have no such function, and are therefore considered the inactive forms of vitamin B12. Health bloggers and the dietary supplement industry have stated that AdoCbl and MeCbl are "more bioavailable" than their inactive counterparts. This claim is unjustified, because the human cell cannot use supplemental or food-derived AdoCbl and MeCbl as coenzymes. **All** forms of B12 that enter a human cell need to be reduced to a core cobalamin molecule $[Co^{2+/1+}]$Cbl by a multiprotein complex. Part of this multiprotein complex is the protein MMACHC that removes the upper ligand of **all** of the Cbl forms and transports it to the regions of the cell in which it will be further processed into an active form [Obeid et al., 2015, Kim et al., 2009, Hannibal et al., 2009]. The multiprotein complex cannot be bypassed by supplemental or food-derived AdoCbl and MeCbl, because the cell has no mechanism to allow such thing.

Now that we know that MeCbl and

AdoCbl follow the same intracellular route of CNCbl and OHCbl, the question remains whether the cells can use the removed ligands of supplemental AdoCbl and MeCbl to reform the biologically active forms. The answer is no, because the methyl and adenosyl components of supplemental MeCbl and AdoCbl are cleaved inside the cells. The methyl-group will be transferred to a negatively charged acceptor, and the adenosyl component is released as a free radical and will be consumed as a co-substrate in the cell or act as a catalyst for other reactions [Obeid et al., 2015, Paul and Brady, 2017, Marsh et al., 2010]. Therefore these two components are not available to be "reattached" to $[Co^{2+/1+}]$Cbl. The intermediate $[Co^{2+/1+}]$Cbl will be methylated in the cytosol or adenosylated in the mitochondria to form MeCbl and AdoCbl respectively.

You may wonder if any of the ligands that are cleaved from the initial supplemental or food-derived form is superior to all the others because it presents any advantages. It can be argued that CNCbl is an inferior choice because the ligand is a cyanide group, and most of us will agree that we should all refrain from cyanide poisoning as much as possible. OHCbl might also be less interesting, because your body accumulates enough of the cleaved ligand, H2O, anyway. The methyl-group that is cleaved from MeCbl can also be derived from foods that contain methionine, one-carbon units and choline [Niculescu and Zeisel, 2002]. The adenosyl component can only be formed by MMACHC and by single-electron reduction of S-adenosylmethionine complexed to an iron-sulfur cluster. So possibly, the cleaved ligand of AdoCbl might be more interesting to the human cells than the cleaved ligands of the other 3 B12 forms, but this topic requires further research.

In conclusion, biochemistry suggests that all B12 forms follow the same pathway of intracellular processing due to their near-identical chemical structures. There is no evidence that suggests any of the B12 forms is easier to digest or process (in individuals without disorders affecting B12 assimilation), nor that AdoCbl and/or MeCbl skip certain steps in the pathway. For your cells, it does not matter which form of vitamin B12 you ingest (although in most cases CNCbl is less advisable), as long as you ingest enough of it.

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