

How Orotates Work The Biochemistry of “Vitamin B13”

by Ed Sharpe

This article addresses two biochemical puzzles about the mineral orotates: how they get into cells and what they do once they're in.

We begin with the fact that the orotate salts are electrically neutral and relatively stable against dissociation, properties that seem to be crucial for the ability of orotates to participate in intracellular mineral uptake and transport. Dissociation is the process that takes place when a salt is dissolved in a solvent such as water and breaks up into its component ions. Table salt dissolved in water, for example, dissociates into sodium and chloride ions. At physiological pH the orotate salts are much more stable than table salt and will not readily dissociate into free orotic acid plus a mineral ion.

Free orotic acid (OA) itself is known to get into cells by simply leaking (diffusing) through cell membranes, rather than by being actively transported. But diffusion is a relatively inefficient process, which limits the amount of OA that can enter a cell. By contrast, uracil—a compound almost identical to OA, only minus the carboxylic acid group—is taken up efficiently by a transporter protein that binds to uracil molecules and drags them into the cell.¹ This transporter appears to be specific for uracil or similar molecules which are uncharged, but not for uracil's close cousin OA (which is negatively charged at body pH).

Bind the orotic acid with a mineral, however, and you end up with a stable electrically neutral salt. This property is just what is needed for OA along with its bound mineral to be taken up directly by the uracil transporter. At the same time, neutralizing the charge on OA makes the resulting complex more lipophilic or “fat-loving” than free OA; as a result, the stable orotate complex would be expected to diffuse more easily through the lipid membranes of cells. Essentially just such a mechanism was proposed by Nieper for enhancing the diffusion of mineral ions across cell membranes.² Either way—via enhanced diffusion or active transport—complexing a mineral with orotate results in increased uptake of both components of the complex by cells.

That's still not the whole story of orotate, however. Here and there in his papers, Nieper gives tantalizing clues about the role of the “pentose phosphate

pathway” or PPP in mediating the effects of his mineral orotates.²⁻⁴ The PPP is a well-known biochemical cycle which, among other vital functions, is responsible for synthesizing D-ribose 5-phosphate. D-ribose is of course the sugar which gets incorporated into nucleotides (a process known as ribosylation) and ultimately into RNA/DNA. Was Nieper attempting to signal a deep connection between the ribosylation of orotate and its activity as a mineral transporter?

The answer is yes. To see what Dr. Nieper was hinting at, we need some additional background information on OA, also known as vitamin B13.

Although orotic acid isn't officially considered a vitamin these days, over 40 years ago it was found to have growth-promoting, vitamin-like properties when added to the diets of laboratory animals. Subsequent nutritional studies in humans and animals revealed that OA has a “sparing” effect on vitamin B12, meaning that supplemental OA can partially compensate for B12 deficiency.^{5,6} OA also appears to have a direct effect on folate metabolism.⁷

Many of the vitamin-like effects of OA are undoubtedly due to its role in RNA and DNA synthesis. (B12 and folate are also involved in DNA synthesis, but at a point downstream from where OA comes in.) Our bodies produce OA as an intermediate in the manufacture of the pyrimidine bases uracil, cytosine, and thymine.^{8,9} Together, these pyrimidines constitute half of the bases needed for RNA/DNA, the other half coming from the purine bases adenine and guanine which are synthesized independently of OA.

The enzyme orotate phosphoribosyltransferase (OPRTase), which is found in organisms ranging from yeast to humans, is responsible for catalyzing the first step in the conversion of orotic acid into uridine. It does so by facilitating the attachment of a ribose plus phosphate group to OA. The net result is the formation of a molecule named OMP (orotidine 5'-monophosphate), which in turn is the immediate precursor to UMP (uridine 5'-monophosphate).

Because the enzyme OPRTase requires magnesium ions for its activity, some researchers wondered whether a magnesium complex of orotic acid might be involved in binding orotate to the enzyme.¹⁰ They found that the true substrate for OPRTase is not orotate itself but rather a magnesium orotate complex. The fact that the complex is electrically neutral compared to the negatively charged orotate ion means that the complex is more easily transportable to the active site of the

enzyme.¹⁰ These researchers suggested that the magnesium complex helps position orotate within the enzyme in the proper orientation for conversion to OMP. In the process the magnesium ion in the complex gets exchanged with the magnesium ion bound to the active site of the enzyme, the net result being that one magnesium ion is released.

So far, so good. Following up on Nieper's hint, we see that orotate—and specifically magnesium orotate—can interact with the pentose phosphate pathway (PPP) to generate OMP and ultimately uridine.^{2, 10} But Nieper also pointed out that the mineral-transport activity of the orotates does not necessarily have anything to do with the formation of RNA or DNA. To resolve this apparent contradiction, we must seek out an additional metabolic role for orotate independent of RNA/DNA synthesis

In fact, not all the uridine formed from orotic acid does wind up in RNA or DNA. There are other vital roles for orotic acid and uridine in the body—for example, OA gets taken up by red blood cells where it is rapidly converted to UDP-glucose by way of OPRTase and other enzymes. Here UDP is the nucleotide uridine diphosphate. The red blood cells can then act as a storage and distribution pool for delivering glucose and uridine to tissues such as brain, heart, and skeletal muscle.² Because UDP-glucose is a precursor for glycogen (a storage form of glucose), the delivery of UDP-glucose to heart muscle and its conversion there to glycogen might account for some of the cardioprotective effects of orotic acid.^{11, 12}

Which brings us right back to Dr. Nieper's work.

Based on the available scientific evidence, it seems clear that magnesium orotate can get channeled directly into OMP synthesis and ultimately into UDP-glucose, which can then resupply a heart under stress with carbohydrates and nucleotides. Thus a mechanism exists for explaining why magnesium orotate works even better than orotic acid for heart conditions.¹¹⁻¹³ In contrast, some of the mineral orotates such as copper and nickel either inhibit OPRTase or, in the case of calcium orotate, neither activate nor inhibit the enzyme.¹⁰ This suggests that the body preferentially uses magnesium orotate for promoting uridine synthesis. In a sense, complexing OA with magnesium magnifies the “vitamin-like” properties of vitamin B13.

Another effect of magnesium orotate is to inhibit the development of atherosclerosis when administered orally to humans¹⁴ or experimental animals.¹⁵ The animal study in particular tells us that magnesium orotate performs better than orotic acid, which in turn outperforms magnesium chloride, in inhibiting atherosclerotic changes caused by high levels of

cholesterol in the diet.¹⁵ In other words, a synergy exists between magnesium and orotic acid such that the complex they form—magnesium orotate—is more potent than either one alone. Dr. Nieper explained this effect by suggesting that when OA in the magnesium orotate complex is coupled with ribose (ribosylated) in the walls of blood vessels, the magnesium ion is liberated during this process and becomes locally available for activating cholesterol-metabolizing enzymes.³

The increase in potency of magnesium in going from a chloride salt to an orotate salt is notable and certainly consistent with Nieper's ideas about orotate as a mineral transporter. But notice that orotic acid also increases in potency in going from free OA to its magnesium complex, an enhancement consistent with the idea that magnesium orotate gets preferentially directed toward uridine synthesis by OPRTase. It is just this combination of properties—enhanced transport of magnesium, itself known¹⁶ for its anti-atherosclerotic and anti-cholesterol effects, and enhanced synthesis of uridine from orotic acid^{9, 10}—that makes magnesium orotate so helpful for treating cardiovascular disorders.

By contrast, the very similar compound calcium orotate has none of the effectiveness of magnesium orotate in lowering serum cholesterol, although it does have other characteristics beneficial for treating arterial disease.² The difference in activity between magnesium and calcium orotate can best be explained by the specific effects of magnesium in activating cholesterol turnover² as well as by the specificity of magnesium orotate—but not calcium orotate—for activating OPRTase.¹⁰

As the preceding example shows, the various mineral orotates are likely to be targeted to distinct metabolic pathways in specific tissues. Another example is provided by an experiment involving lithium metabolism in the brain.¹⁷ Lithium is well known for its ability to moderate manic-depressive illness. In an experiment to evaluate lithium-induced changes in brain metabolism, rats were injected with a solution of lithium chloride daily for two weeks. One hour after the last lithium treatment all rats received an injection of radiolabeled orotic acid into the cerebral ventricles. At various intervals thereafter RNA was extracted from rat brains, separated into fractions, and analyzed for radioactivity. The results showed that lithium increases RNA turnover markedly in brain (but not in other tissues such as liver). The authors suggested that lithium acts at the membrane level and that the effects on RNA metabolism are due to changes in the transport of radiolabeled orotic acid—an explanation entirely consistent with Nieper's idea that lithium combines with OA to yield a transportable complex.

In summary, the evidence tends to support Nieper's criteria for orotate as an electrolyte carrier, namely, (1) a low dissociation constant, (2) an affinity for specific cellular systems or organs, and (3) a metabolic pathway which liberates the transported mineral within the targeted organ or system.¹⁸

References

- [1] Wohlhueter RM, McIvor RS, Plagemann PG. Facilitated transport of uracil and 5-fluorouracil, and permeation of orotic acid into cultured mammalian cells. *J Cell Physiol.* 1980;**104**(3):309-19. [[Abstract](#)]
- [2] Nieper HA. The anti-inflammatory and immune-inhibiting effects of calcium orotate on bradytrophic tissues. *Agressologie.* 1969;**10**(4):349-57. Available as article #CM14 from the A. Keith Brewer International Science Library at (608) 647-6513 or [on the Web](#).
- [3] Nieper HA. The clinical applications of lithium orotate. A two years study. *Agressologie.* 1973;**14**(6):407-11. Available as article #CM12 from the A. Keith Brewer International Science Library at (608) 647-6513 or [on the Web](#).
- [4] Nieper HA. The clinical effect of calcium-diorotate on cartilage tissue, the specific function dependent upon the pentose metabolism of bradytrophic tissue [in German]. *Z prakt Geriatrie.* 1973;**3**(4):82-9. English translation available as article #CM29 from the A. Keith Brewer International Science Library at (608) 647-6513 or [on the Web](#).
- [5] Rundles RW, Brewer SS Jr. Hematologic responses in pernicious anemia to orotic acid. *Blood.* 1958;**13**(2):99-115.
- [6] Moruzzi G, Viviani R, Marchetti M. Orotic acid as a "growth factor" for chickens and its relation to vitamin B12 and methionine [in German]. *Biochem Z.* 1960;**333**:318-27.
- [7] Pasquali P, Landi L, Calderera CM, Marchetti M. Effects of orotic acid on dihydrofolate dehydrogenase and on tetrahydrofolate-dependent enzymes in the chick liver. *Biochim Biophys Acta.* 1968;**158**(3):482-4.
- [8] O'Sullivan WJ. Orotic acid. *Aust N Z J Med.* 1973;**3**(4):417-22.
- [9] Connolly GP, Duley JA. Uridine and its nucleotides: biological actions, therapeutic potentials. *Trends Pharmacol Sci.* 1999;**20**(5):218-25. [[Abstract](#)]
- [10] Dodin G, Lalart D, Dubois JE. Role of magnesium cations in the yeast orotate phosphoribosyltransferase catalyzed reaction. Mechanism of the inhibition by Cu⁺⁺ and Ni⁺⁺ ions. *J Inorg Biochem.* 1982;**16**(3):201-13. [[Abstract](#)]
- [11] Donohoe JA, Rosenfeldt FL, Munsch CM, Williams JF. The effect of orotic acid treatment on the energy and carbohydrate metabolism of the hypertrophying rat heart. *Int J Biochem.* 1993;**25**(2):163-82. [[Abstract](#)]
- [12] Ferdinandy P, Fazekas T, Kadar E. Effects of orotic acid on ischaemic/reperfused myocardial function and glycogen content in isolated working rat hearts. *Pharmacol Res.* 1998;**37**(2):111-4. [[Abstract](#)]
- [13] Rosenfeldt FL. Metabolic supplementation with orotic acid and magnesium orotate. *Cardiovasc Drugs Ther.* 1998;**12**(Suppl 2):147-52. [[Abstract](#)]
- [14] Villanyi P, Votin J, Rahlfs V. Arteriosclerosis, myocardial infarct and blood lipids, their therapeutic modification by magnesium orotate [in German]. *Wien Med Wochenschr.* 1970;**120**(5):76-83.
- [15] Jellinek H, Takacs E. Morphological aspects of the effects of orotic acid and magnesium orotate on hypercholesterolaemia in rabbits. *Arzneimittelforschung.* 1995;**45**(8):836-42. [[Abstract](#)]
- [16] Ouchi Y, Tabata RE, Stergiopoulos K, Sato F, Hattori A, Orimo H. Effect of dietary magnesium on development of atherosclerosis in cholesterol-fed rabbits. *Arteriosclerosis.* 1990;**10**(5):732-7. [[Abstract](#)]
- [17] Dewar AJ, Reading HW. Effect of lithium administration on RNA metabolism in rat brain. *Psychol Med.* 1971;**1**(3):254-9.
- [18] Nieper HA. Recalcification of bone metastases by calcium diorotate. *Agressologie.* 1970;**11**(6):495-502. Available as article #CA21 from the A. Keith Brewer International Science Library at (608) 647-6513 or [on the Web](#).