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Fresh look on old substances – new class of NO-independent regulators of soluble guanylyl cyclase activity and function

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Soluble guanylyl cyclase (sGC) is the recognized receptor for the nitric oxide (NO) messenger molecule. Binding of NO to the heme moiety of sGC activates the enzyme several hundred fold. In addition to NO several NO-independent allosteric regulators can activate the enzyme in heme-dependent (YC-1, BAY 41–2272) or heme-independent (BAY 58–2667) fashions. One of the early recognized NO-independent activators of sGC is protoporphyrin IX, a tetrapyrrole compound that actively substitutes for heme and binds to the heme-deficient sGC.

We investigated the effect of various tetrapyrrole compounds on the activity of soluble guanylyl cyclase. In agreement with previous reports sGC was highly activated by protoporphyrin IX and was not activated by uroporphyrin or billirubin. The enzyme was not activated by cobalt-PPIX or tetrapyrrole porphycene. When corrin-containing compounds were tested, we found that some of them are capable of activating sGC several fold. Pro-vitamin factor B was among the most active corrins. Factor B-dependent activation of sGC was synergistically enhanced by the BAY 41–2272 compound. In the presence of BAY 41–2272 the dose response to factor B was shifted leftward. Measurements performed on isolated rat aortic rings showed that factor B and several other corrins, including vitamin B12, induces a dose-dependent relaxation, although with effective concentrations in the millimolar range. Tested corrins were equally effective in endothelium competent or endothelium denudated rings. In the presence of BAY 41–2272 the effective concentrations of factor B were decreased and efficient relaxations were achieved even with low micromolar amounts of factor B.

Changes in blood pressure of chronically instrumented anesthetized rats were also measured. Intravenous injection of 5 mg/kg of factor B induced a modest and transient decrease of both diastolic and systolic blood pressure, while 15 mg/kg showed a larger and more prolonged response. Decreased blood pressure was associated with increased cardiac output, suggesting vascular relaxation as the underlying mechanism for change in blood pressure. In corroboration with data from aortic ring relaxation, administration of factor B in combination with BAY 41–2272 showed the most profound and prolonged effects in blood pressure decreases. These data suggest that corrin-mediated activation of sGC may be a new approach in regulation of sGC activity and function. The data also suggest that supplementary intake of vitamin B12 may influence sGC-signaling or other treatments based on the modulation of cGMP levels.