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STRUCTURE AND LIPOPHILICITY—THE KEYS TO UNDERSTANDING THE FUNCTION OF PYRUVATE DERIVATIVES FOR ISCHEMIA/REPERFUSION?

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Keywords

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Pyruvate and pyruvate derivatives are a large focus of basic science research due to their ability to decrease inflammation and organ dysfunction in response to injury. In animal models sodium pyruvate (NaPyr) or the anion form pyruvate are known to attenuate myocardial, renal and hepatic organ dysfunction after injury [1–3]. Pyruvate is also associated with improved outcomes after severe shock [4,5]. However, NaPyr is not stable in aqueous solutions and undergoes hydration and condensation reactions that may limit its effectiveness [6].

In an attempt to solve this problem, Dr. Fink's group studied the effects of ethyl pyruvate (EP), a pyruvate derivative, and reported that the effects of EP were superior to pyruvate in a model of intestinal ischemia/reperfusion (I/R) [7]. This group subsequently reported the protective role of EP in models of sepsis and inflammation [8–10]. Now in this manuscript by Cruz and colleagues, the group investigated the underlying mechanisms that might differentiate the protective role of EP and other pyruvate derivatives from pyruvate.

Using a model of acute intestinal I/R, the authors examined the effects of treatment with EP, pyruvate, benzoyl formate (BF) and para-hydroxyphenylpyruvate (two other derivatives of pyruvate). The authors observed that EP and BF were the only two compounds that decreased circulating tumor necrosis factor levels and decreased intestinal hyperpermeability after I/R. Based on their results and the structural compositions of the four compounds, the authors concluded that: 1) the ester linkage of EP or pyruvate is not essential as BF is not an ester but was associated with similar protection as EP; 2) tautomerization of pyruvate or EP is not related to their protective effects as BF does not undergo tautomerization; and 3) the greater lipophilicity of EP may be related to the efficacy of EP in this model. This set of experiments nonetheless leave the readers asking what role might different doses play and would the effects be different if the animals were observed for longer time periods. Nonetheless, the data does indicate that lipophilicity may be a key factor for future investigations.

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Despite the evidence supporting the protective effects of EP in animal models, there is at present only one randomized clinical trial of EP (NCT00107666—clinicaltrials.gov). This trial was designed to evaluate the safety and efficacy of EP treatment in patients undergoing cardiopulmonary bypass. However, this trial was stopped in Phase II due to concerns related to the stability of the proprietary EP formulation used in the trial. Per Fink the drug was safe, but no differences in the reduction of major complications were seen between the placebo and EP treatment group [6]. Unfortunately, this still leaves the unanswered question. Is there a clinical benefit for patients who receive EP treatment?

Given the number of positive studies documenting the protective role of EP, it is clear that the work by this group will continue to pave the way for the potential clinical application of EP or a pyruvate-based derivative. Nevertheless, the paucity of clinical translation of EP to date underscores the difficulties of bringing basic science findings to clinical reality.

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