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Towards the Resurrection of the Delta-Opioid Receptor Antagonists in Haemodynamic Shock Management?

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We refer to the papers by Liu et al. [1] and by Duranteau and Le Manach [2] appeared on Anesthesiology, dealing with the suitable employment of the δ-opioid receptor antagonist ICI 174864 (N,N, diallyl-tyr-aib-aib-phe-leu-OH) in experimental haemorrhagic shock and of δ-opioid receptor antagonists for "buying time" in haemorrhagic shock patients, respectively.

These studies follow what shown by ours in 2005 [3] in rabbits developing hypodynamic systemic shock when the superior mesenteric artery (SMA) was hypoperfused at critical levels representing 25-20% of its mean baseline blood flow. We showed that the selective blockade of cardiovascular δ-opioid receptors by ICI 174864 or naltrindole improved haemodynamics, prevented shock irreversibility and reduced plasma nitric oxide (NO) levels; similar effects were obtained by selective inhibition of inducible NO synthase (iNOS) by AMT (± 2-amino-5,6-dihydro-6-methyl-4H-1,3-thiazine, HCl) but not by blocking opioid receptors other than the δ ones (e.g. the κ_1-receptors by nor-binaltorphimine) or by using drugs like fenoprofen and hydrocortisone [3]. Moreover, leu^5- and met^5-enkephalins (ENK, specific activators of δ-opioid receptors), but not other physiological agonists, impaired haemodynamic function and increased plasma NO levels, when administered intravenously, much more during SMA hypoperfusion (SMAH) than in baseline conditions [3]. Considering that splanchnic artery hypoperfusion had been suggested to play a significant role for the development of haemodynamic shock irreversibility, our experimental model was just assessed to establish the critical levels at which SMAH by itself could induce haemodynamic shock. In addition, splanchnic artery occlusion-reperfusion shock models were thought to not reproduce the cardiac depression and/or local arterial vasoconstriction determining splanchnic *hypoperfusion* during various forms of systemic shock. We found the above effects of SMAH to depend on ENK release from the gut causing hyperactivation of the cardiovascular [3] δ-opioid receptors which, in turn, led to high plasma levels of NO. This plasma NO increase, promoving haemodynamic derangement and shock irreversibility, was explained by both δ-opioid receptor-induced higher iNOS activity and ENK-induced inhibition of kininase II [degrading bradykinin (BK) to inactive peptide] but not of kininase I [3]. In this regard, we demonstrated that BK supplies, following action of kininase I, its C-terminal L-arginine for endothelial NO synthesis [4] and that NO-mediated ENK interactions with the renin-angiotensin and kallikrein-kinin systems play an important role in modulating arterial vasoconstriction and venous dilatation [5-7]. Therefore, we pointed out to be not surprising that the $\delta_{1,2}$-opioid receptor agonist DADLE (D-ala^2, D-leu^5-enkephalin) could be ineffective either in a rat model of lethal haemmorrhagic shock, probably depending on the severe and protracted intestinal hypoperfusion, or in reducing cerebral focal or global ischaemia-reperfusion damage [8,9]. On the other hand, *pharmacological* plasma concentrations of opioid agonists originate a lot of complex interactions with neurotransmitters, neuromodulators, autacoids, ion channels and transduction pathways allowing to eclipse the *physiological* effects of opioid peptides [9,10]. Since pronounced splanchnic artery hypoperfusion occurs in all advanced systemic shock states, we concluded that selective δ-opioid receptor antagonists and/or iNOS inhibitors may prove to be useful in improving shock haemodynamics and metabolic derangement and/or in preventing progression toward shock irreversibility [3].

Side effects and safeness of the clinical handling of ICI 174864 and other selective δ-opioid receptor antagonists as well as of selective iNOS inhibitors remain to be characterized. The only study on this issue is the paper by Long et al. [11] reporting the occurrence of neurological adverse effects in ICI 174864-treated rats so that these Authors conclude for a potential limitation on the clinical employment of such compound [11]. However, the efficacy of δ-opioid receptor antagonists and/or selective iNOS inhibitors in experimental haemodynamic shock models lets reasonably hope that these classes of drugs might result life-saving in an often deadly condition as shock is. Therefore, particular consideration should be addressed to a prompt clinical experimentation targeting the δ-opioid receptor/NO pathway with such kind of drugs in shock patients.

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