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COMMENTARY

A Na^+ channel agonist: a potential cardiotonic agent with a novel mechanism?

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Paradigm shift of pharmacologic therapy for congestive heart failure

Cardiotonic agents are essential for improvement of contractile dysfunction in acute congestive heart failure (CHF) and in aggravating phase of chronic CHF. For almost 220 years, digitalis has been used for the treatment of chronic CHF in spite of its narrow safety margin, arrhythmogenicity and pharmacokinetic drawbacks. While catecholamines have been infused intravenously to improve contractile dysfunction in acute CHF, they are also arrhythmogenic and suffer from energetic disadvantages and drug tolerance by continuous administration. Since the early 1980s, extensive efforts have been made to develop novel cardiotonic agents to replace digitalis and catecholamines (Farah *et al*., 1984). As a result of these efforts, selective phosphodiesterase (PDE) III inhibitors, including amrinone, milrinone, enoximon and olprinone, novel agents such as levosimendan and pimobendan that have myofilament Ca^{2+} sensitizing action (in addition to PDE III inhibition), and an orally useful catecholamine derivative, denopamine, have become clinically available (Endoh, 2002; 2003). These novel agents have been shown to elicit beneficial effects to improve the quality of life (QOL) of CHF patients by ameliorating hemodynamic parameters and exercise capacity, but they have failed to improve the prognosis of chronic CHF patients. Large-scale clinical trials have revealed that some of them even abbreviated the lifespan of patients as seen in the increasing incidence of cardiac sudden death in those being treated with these agents compared with those who received a placebo (e.g., Packer *et al*., 1991). A large paradigm shift of pharmacological treatment of chronic CHF has occurred based on the result of these large-scale clinical trials: from inotropic to cardioprotective therapies without scrutinizing the mechanisms underlying the unexpected outcome, including the mechanisms of action of cardiotonic agents, the doses of agents employed, the methods of administration (continuous or intermittent) and the influence of coadministration with digitalis.

Cardioprotective agents, including angiotensin-converting enzyme (ACE) inhibitors, β-adrenoceptor blocking agents, vasodilators, angiotensin AT_1 receptor antagonists (ARBs) and aldosterone antagonists, have become the mainstays of chronic CHF therapy. These agents suppress the compensatory mechanisms exerted on hemodynamic parameters and cardiovascular remodeling, primarily being triggered by myocardial contractile dysfunction, but do not have cardiotonic action. In the 1990s, efforts to develop novel cardiotonic agents became markedly attenuated and indeed almost ceased following disappointing outcomes of long-term inotropic therapies. The current situation, therefore, remains essentially unchanged, in essence being at the same stage as in the early 1980s, from the respect that there exist no ideal cardiotonic agents and that the development of cardiotonic agents with novel action mechanisms would still provide a great therapeutic impact on the pharmacologic therapy of CHF.

Mechanisms of currently available cardiotonic agents

Currently available cardiotonic agents, such as digitalis, catecholamines and PDE III inhibitors, have been administered to patients with acute heart failure and in an aggravating phase of CHF. These agents induce a positive inotropic effect (PIE) by elevating the intracellular Ca^{2+} ion concentration ($[Ca^{2+}]_i$) through different subcellular mechanisms to lead to an increase in Ca^{2+} transients in myocardial cells; they can be termed Ca^{2+} mobilizers (Endoh, 2003). Among them, catecholamines and PDE III inhibitors act *via* a common signal pathway involving cAMP, while digitalis is unique in that it increases intracellular Na^+ ($[Na^+]_i$) by inhibition of Na^+, K^+ ATPase activity and thereby increasing $[Ca^{2+}]_i$ *via* a Na^+/Ca^{2+} exchanger.

Among the novel agents, levosimendan and pimobendan, which are clinically available in some countries (Cleland *et al*., 2004), are of great interest as they have been shown to increase myofilament Ca^{2+} sensitivity in experimental animals and in ventricular muscle isolated from patients with severe heart failure. However, it has not been established to what extent the Ca^{2+} sensitizing action significantly contributes to their clinical benefit because they have also the PDE III inhibitory action (Endoh, 2003).

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Na^+ channel agonists as potential novel cardiotonic agents

A family of experimental agents, such as veratridine, batrachotoxin, aconitine and pyrethroids, act on activation and/or inactivation of Na^+ (Wang & Wang, 2003). Cardiotonic agents, such as anthopleurin-A, DPI 201-106, BDF 9148, and BDF 9198, act by slowing I_{Na} inactivation (Yuill *et al*., 2000). As well, these agents induce persistent I_{Na}, causing an increase in the net depolarizing current during their action, which produces an extensive prolongation of APD and of QT-interval in ECG, associated with the risk of arrhythmias mediated by early after-depolarization (EAD) (Yuill *et al*., 2000). The risk of arrhythmogenicity makes these agents clinically inapplicable.

Recently, it has become evident that different mechanisms are involved in the modes of action of Na^+ channel agonists, and a potential dissection of the cardiotonic action from arrhythmogenicity could be possible with a novel agent. It has been elucidated that lipid-soluble alkaloid Na^+ channel agonists bind to the receptor in a strongly hydrophobic region of the Na^+ channel to affect the gating parameters of Na^+ channels, and to shift the voltage dependence of activation to a more negative potential and inhibit Na^+ channel inactivation. This results in the persistent activation of a fraction of Na^+ channels at resting membrane potential. Another mechanism of action of Na^+ channel agonists is that pyrethroids increase the window current of cardiac I_{Na}, while fenpropathrin (type II pyrethroid) produces leftward shifts in both activation and inactivation curves of I_{Na}, resulting in a shift of the window current range to a more negative potential. It is postulated that this action might be involved in the generation of EAD in a prolonged plateau phase in cardiac ventricular myocytes (Spencer *et al*., 2001).

In this issue of *British Journal of Pharmacology*, dimethyl lithospermate B (dmLSB) isolated from the root extract of *Salvia miltiorrhiza*, called *danshen* in Asian traditional medicine, has been proposed as a potential cardiotonic agent without arrhythmogenicity (Yoon *et al*., 2004). The effects of dmLSB on I_{Na} are shown to be distinct from those of existing Na^+ channel agonists in that it shifts the activation curve in the positive direction, but has no effect on the steady-state inactivation curve of I_{Na}. Additionally, while dmLSB slows down the inactivation kinetics of I_{Na}, it produces no sustained component of I_{Na}. Prolongation of action potential duration (APD) induced by dmLSB without provoking EADs may be ascribed to these characteristics of I_{Na} kinetics produced by the compound. Considering that the generation of EADs is responsible for arrhythmogenesis by the alkaloid Na^+ channel agonists, the characteristics of the dmLSB-induced effect on I_{Na} are of particular interest; and it will be important to examine whether the lack of generation of EADs with dmLSB results in the lack of or less arrhythmogenic potentials of this compound in experimental animals and patients.

Cardiotonic agents, such as DPI 201-106, and BDF 9148, act by slowing I_{Na} inactivation and also induce persistent I_{Na}, causing an increase in the net depolarizing current during their action, which is associated with the risk of arrhythmias mediated by EADs (Yuill *et al*., 2000). Further, agents, such as DPI 201-106 and BDF 9148, also inhibit $I_{Ca(L)}$ and the inward rectifier K^+ current (Ravens *et al*., 1995). Recently, it was reported that KB130015, a newly developed amiodarone derivative, slowed I_{Na} inactivation without developing persistent I_{Na}, but this compound also suppressed I_{Ca} and consequently abbreviated APD (Macianskiene *et al*., 2003). Since dmLSB does not affect any other ionic currents in cardiac myocytes, its characteristic of acting on the inactivation kinetics of I_{Na} may be more suitable, making it potentially a better cardiotonic agent with less arrhythmogenic potentials compared with other Na^+ channel agonists.

Perspectives for development of novel cardiotonic agents

Cardiotonic agents are classified into three classes based on their subcellular mechanisms of action, that is, agents acting through upstream mechanisms (Ca^{2+} mobilizers), and central and downstream mechanisms (Ca^{2+} sensitizers) (Blinks & Endoh, 1986; Endoh, 1998). Most of the currently available cardiotonic agents belong to the former class, and are generally associated with the risks of producing intracellular Ca^{2+} overload that can lead to induction of arrhythmias, cardiac cell injuries and ultimate cardiac cell deaths. Further, they have energetic disadvantages, requiring activation energy and lose their effectiveness as cardiotonic agents in various pathophysiological conditions, such as ischemia, acidosis and/or CHF. In this respect, Ca^{2+} sensitizers are more attractive as potentially clinically applicable cardiotonic agents (Endoh, 2003). Nonetheless, cardiotonic agents acting through upstream mechanisms, namely acting *via* signaling other than cyclic AMP-mediated processes, are likewise of great interest because digitalis improves the QOL of CHF patients without aggravating prognosis (The Digitalis Investigation Group, 1997). Potential clinical availability of the novel Na^+ channel agonist that acts through upstream mechanisms primarily by modulation of the cellular Na^+ movement and shares in part the same mechanism of action of digitalis remains unsettled and is a worthy subject to be pursued in further study.

References

BLINKS, J.R. & ENDOH, M. (1986). Modification of myofibrillar responsiveness to Ca^{++} as an inotropic mechanism. *Circulation,* **73,** III85–III98.

CLELAND, J.G.F., NIKITIN, N. & MCGRWAN, J. (2004). Levosimendan: first in a new class of inodilator for acute and chronic severe heart failure. *Expert Rev. Cardiovasc.,* **2,** 9–19.

ENDOH, M. (1998). Regulation of myocardial contractility by a downstream mechanism. *Circ. Res.,* **83,** 230–232.

ENDOH, M. (2002). Mechanism of action of novel cardiotonic agents. *J. Cardiovasc. Pharmacol.,* **40,** 323–338.

ENDOH, M. (2003). The therapeutic potential of novel cardiotonic agents. *Expert Opin. Invest. Drugs,* **12,** 735–750.

FARAH, A.E., ALOUSI, A.A. & SCHWARZ JR, R.P. (1984). Positive inotropic agents. *Annu. Rev. Pharmacol. Toxicol.,* **24,** 275–328.

MACIANSKIENE, R., BITO, V., RAEYMAEKERS, L., BRANDTS, B., SIPIDO, K.R. & MUBAGWA, K. (2003). Action potential changes associated with a slowed inactivation of cardiac voltage-gated sodium channels by KB130015. *Br. J. Pharmacol.,* **139,** 1469–1479.

PACKER, M., CARVER, J.R., RODEHEFFER, R.J., IVANHOE, R.J., DIBIANCO, R., ZELDIS, S.M., HENDRIX, G.H., BOMMER, W.J., ELKAYAM, U., KUKIN, M.L., MALLIS, G.J., SOLLANO, J.A., SHANNON, J., TANDON, P.K. & DE METS, D.L. (1991). Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N. Engl. J. Med.,* **325,** 1468–1475.

RAVENS, U., AMOS, G.J., EHRING, T. & HEUSCH, G. (1995). BDF 9148 – a sodium channel modulator with positive inotropic action. *Cardiovasc. Drug Rev.,* **3,** 260–274.

SPENCER, C.L., YUILL, K.H., BORG, J.J., HANCOX, J.C. & KOZLOWSKI, R.Z. (2001). Actions of pyrethroid insecticides on sodium currents, action potentials, and contractile rhythm in isolated mammalian ventricular myocytes band perfused hearts. *J. Pharmacol. Exp. Ther.,* **298,** 1067–1082.

THE DIGITALIS INVESTIGATION GROUP (1997). The effect of digoxin on mortality and morbidity in patients with heart failure. *N. Engl. J. Med.,* **336,** 525–533.

WANG, S.Y. & WANG, G.K. (2003). Voltage-gated sodium channels as primary targets of diverse lipid-soluble neurotoxins. *Cell. Signal.,* **15,** 151–159.

YOON, J.-Y., AHN, S.-H., OH, H., KIM, Y.-S., RYU, S.Y., HO, W.-K. & LEE, S.-H. (2004). A novel Na^+ channel agonist, dimethyl lithospermate B, slows Na^+ current inactivation and increases action potential duration in isolated rat ventricular myocytes. *Br. J. Pharmacol.,* (in press).

YUILL, K.H., CONVERY, M.K., DOOLEY, P.C., DOGGRELL, S.A. & HANCOX, J.C. (2000). Effects of BDF 9198 on action potentials and ionic currents from guinea-pig isolated ventricular myocytes. *Br. J. Pharmacol.,* **130,** 1753–1766.