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LETTER TO THE EDITOR

Letter to the Editor re Mani et al.

Linked Articles
To view the original paper by Mani *et al.* visit http://dx.doi.org/10.1111/j.1476-5381.2011.01273.x and to view the reply to this letter visit http://dx.doi.org/10.1111/j.1476-5381.2011.01457.x

To the Editor:

We have read with interest the recent article published by the *British Journal of Pharmacology* entitled 'Activation of vascular KCNQ (K_v7) potassium channels reverses spasmogen-induced constrictor responses in rat basilar artery' (Mani *et al.*, 2011). The study adds to a mounting body of evidence suggesting a pivotal role for KCNQ (K_v7) channels in regulating vascular tone and more particularly cerebral blood flow. Mani *et al.* (2011) showed that a known K_v7 activator flupirtine, as well as celecoxib, a type 2 cyclooxygenase -specific inhibitor clinically used as an anti-inflammatory that has recently been shown to also stimulate K_v7 channels (Brueggemann *et al.*, 2009), relaxed 5HT-contracted basilar arteries and increased voltage-gated potassium currents in isolated myocytes.

Due to the relative infancy of the vascular KCNQ field, it is important that previous literature on this topic is adequately represented. Since the initial discovery in mouse portal vein myocytes (Ohya *et al.*, 2003), KCNQ gene expression has been described in range of rodent blood vessels including portal vein, aorta, carotid, pulmonary and mesenteric arteries (Yeung *et al.*, 2007; Mackie *et al.*, 2008; Joshi *et al.*, 2009; Zhong *et al.*, 2010a) as well as human blood vessels (Ng *et al.*, 2011) where products of KCNQ1, KCNQ4 and KCNQ5 predominate. In addition, a functional role for K_v7 channels in controlling vascular tone development has been identified using K_v7 channel blockers, which inhibit endogenous K^+ currents, depolarize vascular smooth muscle and increase contractility (Yeung and Greenwood, 2005; Mackie *et al.*, 2008; Joshi *et al.*, 2009; Zhong *et al.*, 2010a; Ng *et al.*, 2011). This has been corroborated by the observation that agents such as the anticonvulsant retigabine, acrylamide S-1 and maxiprost, which activate $K_v7.2$–7.5 in overexpression systems, also enhance endogenous K^+ in various vascular myocytes (Mackie *et al.*, 2008; Yeung *et al.*, 2008; Joshi *et al.*, 2009; Zhong *et al.*, 2010a) and relax pre-contracted vessels (Yeung *et al.*, 2007; Mackie *et al.*, 2008; Yeung *et al.*, 2008; Joshi *et al.*, 2009; Zhong *et al.*, 2010a; Ng *et al.*, 2011). Hence, the work by Mani *et al.* (2011) represents an addition to the burgeoning data showing K_v7 channels to be key regulators of vascular tone.

Much of the basilar artery data presented in Mani *et al.* confirm the observations made by Zhong *et al.* (2010a) who utilized extensive q-PCR, immunocytochemistry, isobaric myography and single-cell electrophysiology to characterise the importance of KCNQ channels in the rat middle cerebral artery. The impact of both sets of data is considerably enhanced when the reader fully appreciates that KCNQ channels contribute to control of contraction in conduit and myogenic resistance cerebral vessels and represent an important potential therapeutic target for the treatment of vascular disease. However, one note of caution raised by Zhong *et al.* (2010a) was ignored by Mani *et al.* (2011). Similar to previous studies on various vascular smooth muscles (Yeung and Greenwood, 2005; Yeung *et al.*, 2007; Mackie *et al.*, 2008; Joshi *et al.*, 2009), Panels A and B of figure 3 in Mani *et al.* (2011) show that 10 μM XE991 evoked depolarization of isolated basilar arterial myocyte artery and constriction of intact basilar arteries. The authors concluded that this may be attributed to the inhibition of K_v7 channels. However, Zhong *et al.* (2010a) showed that XE991 completely suppressed native K_v currents of rat middle cerebral arterial myocytes and inhibited heterologously expressed $K_v1.2$/$K_v1.5$ and $K_v2.1$/ $K_v9.3$ channels that also contribute to the native K_v current and control of membrane potential in these cells (Albarwani *et al.*, 2003; Chen *et al.*, 2006; Zhong *et al.*, 2010b). Thus, while XE991 is an effective blocker of KCNQ-encoded K^+ channels, caution should be exercised in the interpretation of experiments employing this agent, as it may have additional effects beyond specific blockade of K_v7 channels.

This letter should not be viewed as a negative comment on the data in Mani *et al.* who have contributed significantly to this nascent research field. On the contrary, we hope it emphasizes the perspective in which the article resides and provides further sources of information for this important and emerging aspect of vascular biology.

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