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COMMENTARY

$GABA_B$ receptors in the bladder and bowel: therapeutic potential for positive allosteric modulators?: Commentary on Kalinichev *et al.*, Br J Pharmacol 171: 995–1006

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This article is a Commentary on Kalinichev M, Palea S, Haddouk H, Royer-Urios I, Guilloteau V, Lluel P, Schneider M, Saporito M and Poli S (2014). ADX71441, a novel, potent and selective positive allosteric modulator of the GABAB receptor, shows efficacy in rodent models of overactive bladder. Br J Pharmacol 171: 995–1006. doi: 10.1111/bph.12517

This is a Commentary on an article in BJP by Kalinichev *et al.* (2014). Overactive bladder is a disorder caused in part by urothelial dysfunction, increased excitability of the detrusor and abnormal functioning of neuronal circuits serving the micturition reflex. Kalinichev *et al.* (2014) show that the $GABA_B$ receptor positive allosteric modulator, ADX71441 improves micturition indices and cystometry variables in two separate models of overactive bladder. However, $GABA_B$ receptors are widely expressed at other peripheral sites, including the gastrointestinal tract. Apart from their close anatomical relationship, the bladder and bowel share similarities in function and the central processing and perception of afferent activity from each organ converge on the same brain regions. Moreover, the bladder and bowel display similar visceral pathologies, in particular bladder pain syndrome and irritable bowel syndrome, which can overlap in individual patients. The data presented by Kalinichev *et al.* (2014) demonstrate promise for positive allosteric modulators of $GABA_B$ receptors in regulating bladder function, and hints at their effectiveness in visceral pain. Here, we consider the possibility that $GABA_B$ receptor positive allosteric modulators may similarly influence gastrointestinal function and sensory signalling.

In the paper in question, Kalinichev *et al.* (2014) show that modulation of $GABA_B$ receptors with the $GABA_B$ receptor positive allosteric modulator, ADX71441, significantly affected bladder function in two separate models of overactive bladder, overhydrated mice challenged with furosemide and, in guinea pigs, a model of overactive bladder induced by acetic acid, improving micturition indices and cystometry variables. These authors did not discriminate between peripheral and central effects of ADX71441 on bladder function. However, given the pharmacological effects of the $GABA_B$ receptor agonist, baclofen on contractility in isolated bladder tissues (Santicioli *et al.*, 1986; Sanger *et al.*, 2002), it is quite likely that the $GABA_B$ receptor positive allosteric modulator, ADX71441, may have influenced bladder contractility *locally*. Regardless of its site of action, the effects of ADX71441 reported by Kalinichev *et al.* (2014) support the need for further characterization of the peripheral effects of $GABA_B$ receptor positive allosteric modulators in the bladder, in addition to their effects on the gastrointestinal tract.

These results of Kalinichev *et al.* (2014) have raised some fascinating questions. In particular these authors mentioned (unpublished data) that ADX71441 reduced acute visceral pain in the acetic acid writhing test. This tantalizing

comment should be a powerful stimulus for future investigations of the effects of $GABA_B$ receptor positive allosteric modulators in visceral pain disorders. In this regard, intrathecal injection of the $GABA_B$ agonist, baclofen, reduced the threshold response to colorectal distension in a dose-dependent manner in rats (Hara *et al.*, 1999), implicating $GABA_B$ receptors as important regulators of colonic sensation. Moreover, in a more recent study, the $GABA_B$ receptor positive allosteric modulator, CGP7930, inhibited visceral pain associated with repetitive noxious colorectal distension following its intravenous administration in rats (Brusberg *et al.*, 2009). In this study, however, colonic accommodation was unaffected, perhaps suggesting that CGP7930 did not influence the peripheral $GABA_B$ receptors involved in muscle relaxation.

Another question generated by the article of Kalinichev *et al.* (2014) is its relevance to bladder pain. The bladder pain syndrome (or interstitial cystitis/painful bladder syndrome) is a spectrum of urological symptoms characterized by frequency, urgency and pain on bladder filling. Of further note is the co-morbidity between bladder pain syndrome and other functional pain syndromes, in particular, irritable bowel syndrome (Kim and Chang, 2012), a functional gastrointestinal disorder associated with visceral abdominal pain and altered bowel habit. Kalinichev *et al.* (2014) demonstrated that ADX71441 robustly blocked acetic acid-induced bladder overactivity in the guinea pig, a model of bladder overactivity associated with activation of C-afferent fibres, which are normally silent during physiological bladder distension (de Groat and Yoshimura, 2010). In this context, it should be noted that the $GABA_B$ receptor agonist, baclofen, decreased spinal cord expression of the early gene product, c-Fos, in response to colonic inflammation (Lu and Westlund, 2001). One could speculate that similar pathways were inhibited in the acetic acid-induced model of overactive bladder, used by Kalinichev *et al.* (2014).

Considerations of pain and its suppression inevitably lead to the question of central or peripheral action of ADX71441, in the results of Kalinichev *et al.* (2014). The development of dribbling incontinence described by these authors may lend further support for a contribution of central $GABA_B$ receptors in the modulation of bladder function in the acetic acid-induced model of overactive bladder. A similar response was previously observed following intrathecal administration of baclofen to rats (Watanabe *et al.*, 1997). Moreover, $GABA_A$ receptors, rather than $GABA_B$ receptors, have been implicated in the peripheral inhibition of guinea pig bladder contractility (Kusunoki *et al.*, 1984; receptor nomenclature follows Alexander *et al.*, 2013a, b). Collectively, therefore, given the effects of $GABA_B$ receptor positive allosteric modulators on bladder function (Kalinichev *et al.*, 2014), acetic acid-induced visceral pain (M.Kalinichev, unpubl. data) and colonic visceral pain (Brusberg *et al.*, 2009), it is tempting to speculate that $GABA_B$ receptor positive allosteric modulators may display efficacy in not only functional pain disorders of the bladder, but also of the bowel, through modulation of either central and peripheral $GABA_B$ receptors, or both. Convergence of sensory information in the spinal cord and brain underlies the central mechanisms of colon-bladder cross-sensitization, and potentially the development of colon-bladder co-morbidities in humans (Malykhina *et al.*, 2012). Thus, modulation of $GABA_B$ receptors may not only be efficacious in functional pain disorders of the bladder and bowel individually, but may also prevent cross-sensitization from occurring, and the subsequent development of co-morbid bladder and bowel disorders.

A final but very important consideration is the translational relevance of the results provided by Kalinichev *et al.* (2014). These authors clearly demonstrated a positive effect for $GABA_B$ receptor modulation by ADX71441 in the context of increased micturition or overactive bladder in the mouse and guinea pig respectively. However, these data are of potential significance beyond the bladder, not only in the regulation of gastrointestinal motility, in which $GABA_B$ receptors play a significant role (Hyland and Cryan, 2010), but also in the regulation of other gastrointestinal functions influenced by $GABA_B$ receptors, for example, gastric motility, gastric acid production, intestinal ion transport and epithelial proliferation (Hyland and Cryan, 2010). In addition, a most exciting avenue for future investigation of positive allosteric modulators of $GABA_B$ receptors is in the area of visceral sensation, and the application of these ligands to treat functional pain disorders that are common to both bladder and bowel. The critical feature that will determine the superiority of ADX71441 over the classical direct $GABA_B$ receptor agonists, such as baclofen, will be its side-effect profile. Encouragingly, however, ADX71441 had fewer effects on locomotor function than baclofen, at least in mice (unpubl. data cited in Kalinichev *et al.* 2014). Further fuller data on this crucial aspect of the actions of ADX71441 are awaited.

Conflict of interest

None.

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