Capsaicin receptor antagonists: a promising new addition to the pain clinic

Capsaicin is the pungent vanilloid found in chilli peppers. Sensitivity to this substance has been used for many years to identify nociceptive fibres. These are predominantly unmyelinated C fibres with slow conduction velocity but also a small number of myelinated Aβ fibres. The cell bodies of these fibres lie in the dorsal root and trigeminal ganglia. The latter is involved in the pathogenesis of migraine. It is now well established that capsaicin activates a specific member of the transient receptor potential ligand-gated ion channel family, TRPV1 (previously known as the vanilloid receptor, VR1). The endogenous activators for this receptor are noxious heat (>43°C), protons (acidosis, pH 5–6), the endocannabinoid anandamide, and a range of other putatives including NADA (N-arachidonoyl-dopamine). There is also evidence for a central role of TRPV1 receptors including an interaction with dopaminergic neurones. The roles and activators of TRPV1 receptors have been the subject of reviews.1-5 The polymodal activation profile in response to heat and acidosis, coupled with modulation by several other inflammatory mediators, especially prostaglandins and bradykinin, has led to TRPV1 receptors being described as integrators of inflammatory signalling.5 TRPV1 receptor activation leads to an influx of Ca2+ and prolonged application of an agonist, such as capsaicin, leads to release of central transmitters (glutamate and substance P) from nociceptive afferents and a desensitization of the channel. As a consequence of exhaustion of transmitters and desensitization, the afferent becomes ‘chemically denervated’ and functionally silent. This is the basis for the well-established use of capsaicin cream in clinical settings where efficacy has been reported in osteoarthritis, diabetic neuropathy, and psoriasis.7 There is also evidence of effectiveness in post-herpetic neuralgia and post-mastectomy pain.7,8 The problem with capsaicin, as is well known, is that application produces an intense burning sensation and thus compliance can be a problem (Table 1).

There is now a body of evidence in support of TRPV1 receptor up-regulation in disease. For example, in experimental animals, there is an up-regulation in inflammatory hyperalgesia,9 osteoarthritis,10 and cancer-induced bone pain (see below). Interestingly, in animals with genetic deletion of TRPV1 receptors, the symptoms of experimental arthritis are reduced.11 In this case, deletion of the receptor represents an extreme form of ‘antagonism’. In humans, there are data showing up-regulation of TRPV1 in a wide range of conditions including inflamed bowel, vulvodynia, mastalgia, neurogenic bladder,4,5 and dental pulp inflammation.12 This up-regulation of receptor numbers and function, coupled with initial irritation when using TRPV1 agonists (like capsaicin) and the limited agonist formulation options (e.g., topical cream), forms the basis on which the antagonist strategy has been developed.

In this issue of the British Journal of Anaesthesia, Niyama and colleagues13 describe the use of the selective TRPV1 antagonist SB-366791 [N-(3-methoxyphenyl)-4-chlorocinnamide] in an animal model of bone cancer pain. Mice were injected with NCTC 2472 osteolytic sarcoma cells directly into the femur and then assessed over a 2 h period for pain-related behaviours (limb use, spontaneous

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References:
6 Available from http://www.rcoa.co.uk/

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Editorial II

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The authors have also demonstrated an up-regulation of likely to be the cause of the reduced morphine efficacy. In various stages of clinical evaluation, used in urology via intravesical instillation. Efficacy is questionable at best. Clinical trials summarized in the work of Szallasi and colleagues and from Glenmark and AstraZeneca. Numbers needed to treat (NNT with 95% confidence interval). The authors have previously shown with all doses tested. The authors have previously shown with all doses tested. SB-705498 (0.1, 0.3, and 1 mg kg\(^{-1}\)) was ineffective, resulted in morphine antinociception at SB-366791 at a dose of 0.1 mg kg\(^{-1}\). TRPV1 antagonism in human pain. There are now a wide range of such molecules in various stages of development. From an anaesthetic perspective, this interesting paper is in clinical development. Some of the other TRPV1 antagonists currently in clinical development are noted in Table 1, but there is little published information. These antagonists include GRC6211 (Glenmark) which is in phase II trials for osteoarthritic pain, incontinence, and neuropathic pain, AZD1386 (AstraZeneca) in phase II for chronic nociceptive pain and phase I for gastroesophageal reflux disease, and NGD8243 (Neurogen Corporation) in phase II for cough. From an anaesthetic perspective, this interesting paper should be viewed in the wider context of TRPV1 antagonists as a novel class of analgesic agents. As TRPV1 receptors ‘integrate’, pain signalling antagonizing this receptor should have activity at a range of pains including chronic pain. In addition, as the paper suggests, TRPV1 antagonism may breathe new life into morphine. There are now sufficient data on TRPV1 receptor antagonists to suggest that they have a promising future in the pain clinic.

### Table 1: Comparison of TRPV1 agonist and antagonist strategies for use in the clinic.

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Antagonist</th>
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<tbody>
<tr>
<td><strong>Mode of action</strong></td>
<td>Inhibition of up-regulated TRPV1 receptors activated during inflammation*</td>
</tr>
<tr>
<td><strong>Clinical drugs</strong></td>
<td>SB-705498, NDG8243, AGM517, GRC6211, and AZD1386</td>
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<tr>
<td><strong>Clinical indications</strong></td>
<td>SB705498 phase II migraine, phase I dental pain*</td>
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<td></td>
<td>NGD8243 phase II cough†</td>
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<td></td>
<td>AMG517 phase I pain*</td>
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<tr>
<td></td>
<td>GRC6211 phase II range of pains including osteoarthritis, dental, and neuropathic pain*</td>
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<tr>
<td></td>
<td>AZD1386 phase II chronic nociceptive pain†</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Antagonism of all TRPV1 signalling</td>
</tr>
<tr>
<td></td>
<td>Intense burning leading to reduced compliance</td>
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<tr>
<td></td>
<td>No oral formulation</td>
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<tr>
<td></td>
<td>(Studies difficult to blind)</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>No initial irritation</td>
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<td></td>
<td>Oral formulation</td>
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<td></td>
<td>Potential for good compliance</td>
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Flinches, and weight-bearing). Animals received intraperitoneal morphine (1, 3, and 10 mg kg\(^{-1}\)) or intraperitoneal SB-366791 (0.1, 0.3, and 1 mg kg\(^{-1}\)) alone, or in various combinations. Sarcoma implantation produced an increase in pain-related behaviours. Morphine was effective only at the higher dose of 10 mg kg\(^{-1}\) and SB-366791 was effective alone at 0.3 and 1 mg kg\(^{-1}\). Importantly, SB-366791 at a dose of 0.1 mg kg\(^{-1}\), which on its own was ineffective, resulted in morphine antinociception at all doses tested. The authors have previously shown with this model that \(\mu\) opioid receptors on TRPV1 positive afferents are down-regulated. This down-regulation is likely to be the cause of the reduced morphine efficacy. The authors have also demonstrated an up-regulation of TRPV1 receptors and have therefore suggested that reduced morphine efficacy could be rescued by switching off up-regulated TRPV1 receptors. Although SB-366791 is an interesting experimental tool, antagonists suitable for clinical development are required to evaluate the role of TRPV1 antagonism in human pain. There are now a wide range of such molecules in various stages of development (Table 1).

SB-705498 (\(N-(2\text{-bromophenyl})-N\)\(^\text{\prime}\)-(\((\text{R})-1\text{-}(5\text{-trifluoromethyl}-2\text{-pyridy1)}\text{pyrrolidin-3-yl})\text{urea}\)) is a novel, selective (screened against 39 targets), and potent TRPV1 antagonist capable of inhibiting capsaicin, acid, and heat-evoked activation. In addition, this antagonist displayed good oral bioavailability in rat, guinea pig, and dog. When administered to healthy human volunteers, a single oral dose of 400 mg (the study used a variety of doses up to 400 mg) resulted in peak plasma concentrations of \(~1.2\ \mu\text{g ml}^{-1}\) some 0.75–4 h after dosing. In this pharmacokinetic analysis, the most common adverse reaction was headache (31.6% in treatment and 15.8% in placebo), but others included contact dermatitis (10.5% in treatment and 21.1% in placebo; the authors attribute dermatitis to application of dressings/ECG electrodes) and dizziness (5.3% in both groups). These were not dose-related. SB-705498 was effective against UVB irradiation-induced thermal pain, sensitization, and flare and capsaicin-evoked hyperalgesia and flare in volunteers. There are phase II clinical trials of this antagonist in migraine, dental pain, and irritable bowel syndrome (terminated for the latter indication). A further orally active antagonist (SB-782443) (GlaxoSmithKline) is in clinical development. Some of the other TRPV1 antagonists currently in clinical development are noted in Table 1, but there is little published information. These antagonists include GRC6211 (Glenmark) which is in phase II trials for osteoarthritic pain, incontinence, and neuropathic pain, AZD1386 (AstraZeneca) in phase II for chronic nociceptive pain and phase I for gastroesophageal reflux disease, and NGD8243 (Neurogen Corporation) in phase II for cough.

### Declaration of Interest

As part of a TRPV1 collaboration with GSK, DGL has received research reagents and used the R&D facility in Harlow. Work on TRPV1 receptors in his laboratory has been funded by British Journal of Anaesthesia/Royal College of Anaesthetists.
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References
1 Szallasi A, Blumberg PM. Vanilloid (Capsaicin) receptors and mechanisms. Pharmacol Rev 1999; 51: 159–212
3 Szallasi A. Small molecule vanilloid TRPV1 receptor antagonists approaching drug status: can they live up to the expectations? Naunyn Schmiedebergs Arch Pharmacol 2006; 373: 273–86
6 Available from www.medicine.ox.ac.uk/bandolier/band29/b29-6.html
8 Available from http://gsk-clinicalstudyregister.com/protocolcomp_list.jsp?compound=Sb705498&studyType=All&phase=All&population=All&marketing=All&status=All&country=All
10 Available from http://gsk-clinicalstudyregister.com/protocolcomp_list.jsp?compound=SB705498&studyType=All&phase=All&population=All&marketing=All&status=All&country=All
16 Available from http://www.neurogen.com/products/vr1index.htm