Received: 8 September 2019 | Revised: 8 November 2019 | Accepted: 19 November 2019

DOI: 10.1111/bph.14952

REVIEW ARTICLE

Interventions in the B-type natriuretic peptide signalling pathway as a means of controlling chronic itch

Jianghui Meng[1,2,3] | Weiwei Chen[1] | Jiafu Wang[1,3]

[1]School of Life Sciences, Henan University, Henan, China

[2]National Institute for Cellular Biotechnology, Dublin City University, Dublin, Ireland

[3]School of Biotechnology, Faculty of Science and Health, Dublin City University, Dublin, Ireland

Correspondence
Jianghui Meng and Jiafu Wang, School of Biotechnology, Faculty of Science and Health, Dublin City University, Glasnevin, Dublin 9, Ireland.
Email: jianghui.meng@dcu.ie; jiafu.wang@dcu.ie

Funding information
Science Fundation Ireland (SFI), Grant/Award Numbers: 13/CDA/2093 to J.W.., 17/TIDA/4977 to J.W.., Grant Number 15/SIRG/3508T to J.M.; SFI Investigators' Awards, Grant/Award Numbers: 17/TIDA/4977, 13/CDA/2093, 15/SIRG/3508T

Chronic itch poses major health care and economic burdens worldwide. In 2013, B-type natriuretic peptide (BNP) was identified as an itch-selective neuropeptide and shown to be both necessary and sufficient to produce itch behaviour in mice. Since then, mechanistic studies of itch have increased, not only at central levels of the spinal relay of itch signalling but also in the periphery and skin. In this review, we have critically analysed recent findings from complementary pharmacological and physiological approaches, combined with genetic strategies to examine the role of BNP in itch transduction and modulation of other pruritic proteins. Additionally, potential targets and possible strategies against BNP signalling are discussed for developing novel therapeutics in itch. Overall, we aim to provide insights into drug development by altering BNP signalling to modulate disease symptoms in chronic itch, including conditions for which no approved treatment exists.

1 | INTRODUCTION

Chronic itch is a major symptom of numerous dermatological and systemic diseases. It substantially impairs patients' quality of life resulting in considerable socio-economic costs. Current treatment options for chronic itch are limited and do not treat the underlying causes of itch, so there is a major need to develop novel effective treatments. Neuropeptides mediating itch are released by dedicated sensory C-fibres in response to a range of environmental factors and their release elicits a scratching behavioural response rather than withdrawal. Given that itch is a significant clinical problem affecting a large global population, it is necessary to discuss the recent findings about itch-related neuropeptides and their signalling in itch transmission. Several itch neuropeptides have been discovered in recent years, including gastrin releasing peptide (GRP), B-type natriuretic peptide (BNP, also known as natriuretic polypeptide b [Nppb], encoded by the *Nppb* gene), and neuromedin B (Nmb; Koga et al., 2011; Mishra, Holzman, & Hoon, 2012; Mishra & Hoon, 2013; Sukhtankar & Ko, 2013; Sun et al., 2009; Sun & Chen, 2007). Because BNP is an important itch-selective neuropeptide in central and peripheral systems, the function of BNP in itch transmission has become an interesting and intensive research field. Selective targeting of the BNP signalling pathway provides a potential for itch treatment.

Abbreviation: AD, atopic dermatitis; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; DRG, dorsal root ganglion; GC, guanylyl cyclase; GRP, gastrin releasing peptide; HDM, house dust mite; ISH, in situ hybridization; phKCs, primary human keratinocytes; S1P, sphingosine-1 phosphate; scfv, single-chain variable fragment; SNAP-25, synaptosome-associated protein 25 kDa; SNARE, soluble N-ethylmaleimide-sensitive factor activating protein receptor; TG, trigeminal ganglia; TGN, trigeminal ganglion neurons; VAMP, vesicle-associated membrane protein.

2 | ORIGIN OF BNP AND ITS FUNCTION

BNP is a 32 amino-acid cyclic peptide that was initially discovered in extracts of porcine brain. It is released predominantly from cardiac ventricles (Minamino, Aburaya, Ueda, Kangawa, & Matsuo, 1988; Minamino, Kangawa, & Matsuo, 1988) and is homologous to, but clearly distinct from, atrial natriuretic peptide (ANP) in terms of the amino acid sequence (Chinkers & Garbers, 1989; Maekawa et al., 1988; Minamino, Kangawa, & Matsuo, 1988; Seilhamer et al., 1989;

Sugimoto, Shigemi, Okuno, Yawata, & Morimoto, 1989). As it was later established that cardiomyocytes mainly produce BNP, BNP was renamed "B-type natriuretic peptide," from its previous name of "brain natriuretic peptide." BNP plays significant roles in cardiac embryogenesis, maintaining cardiovascular homeostasis and regulating blood pressure (Potter, Yoder, Flora, Antos, & Dickey, 2009; Woodard & Rosado, 2007). Ablation of *Nppb* triggers hypertension and cardiovascular dysfunction and results in reduced itch response to many pruritogens (Table 1). Deletion of **natriuretic peptide receptor type A** gene (*NprA*) in mice causes hypertension and leads to cardiac hypertrophy with increased cardiac mass, fibrosis, and inflammation (Table 1). In dilated cardiomyopathy, increased BNP levels were significantly related to the disease severity (Noori, Mahjoubifard, Shahramian, Teimouri, & Jahangirifard, 2015; Noori, Teimouri, & Shahramian, 2017). Three receptors (**NPRA**, **NPRB**, and **NPRC**) have been identified for BNP, with differing selectivity. NPRA binds to **ANP** > BNP > > **CNP**, whereas NPRB binds to CNP > ANP > BNP, and the clearance receptor, NPRC, binds all natriuretic peptides equally. These three receptors show different distribution in the body (Table 1). NPRA is a homodimeric membrane guanylyl cyclase expressed in a variety of tissues (Table 1). BNP, upon binding to NPRA, leads to an increase of the intracellular secondary messenger, cGMP (Huntley et al., 2006), and further stimulates three known cGMP effector molecules: cGMP-dependent PKGs, cGMP-dependent PDEs, and cGMP-dependent ion channels. These cascade events produce anti-hypertensive, anti-hypertrophic, and anti-fibrotic effects. Thus, analogues of BNP have been designed in order to reproduce the beneficial effects of NPRA activation in patients with chronic heart failure. In sensory neurons, cGMP permits signal modulation, amplication, and encoding, before depolarization (Gao et al., 2015).

Later on, BNP was detected in retina, where it suppresses **$GABA_A$ receptor**-mediated current of ON-type rod-dominant bipolar cells in the rat (Cao, Zhou, & Yang, 2008; Yu, Cao, & Yang, 2006; Table 1). Thus far, BNP has been detected in many tissues (Table 1). In embryonic stem cells, BNP signalling leads to the down-regulation of **$GABA_A$ receptor** genes and, in turn, suppresses the phosphorylation of the histone H2AX to γ-H2AX. As a result, activation of embryonic stem cell proliferation occurs (Abdelalim & Tooyama, 2009; Table 1). In other pathways, BNP activates NPRB and the transcription factor Ets-1, which may enhance the proliferation and survival of embryonic stem cells (Abdelalim & Tooyama, 2009; Table 1).

3 | DIFFERENTIAL EXPRESSION OF BNP AND ITS RECEPTORS IN PERIPHERAL AND SPINAL CORD NEURONS UNDERLIES THEIR CONTRIBUTIONS TO ITCH

BNP is expressed in the sensory ganglia including DRGs and TGNs but barely expressed in the dorsal horn of the spinal cord (Table 2). Moreover, NPRA, B, C are found in sensory ganglia including DRGs, TGs, and in the spinal cord (Mishra & Hoon, 2013; Zhang et al., 2010; Table 2). However, a more detailed characterization revealed their differential localization, for example, TRPC channels may not express in sensory neurons but it exists in the associated non-neuronal cells in the ganglia (Table 2).

The presence of BNP in sensory ganglia has attracted extensive attention especially in itch and pain study. Using the large-scale single RNA sequencing of mice DRGs, the sensory neurons have been divided into three molecularly different groups, NP1, NP2, and NP3. Among them, NP1 neurons express GPCR **Mas-related Gpr family member** D (MrgprD) to transmit chemical itch, for example, the itch induced by β-alanine, and lysophosphatidic acid-associated cholestatic disorders, as well as light punctate mechanical information. NP2 neurons are characterized by the expression of MrgprA3 and MrgprC11 which also transmit chemical-induced itch and mediate chloroquine- and histamine-associated acute itch, but not related to pain sensitivity. NP3 neurons are $Nppb^+$ neurons, and these neurons express the **IL-31 receptor α** (IL-31Rα) and **oncostatin M receptor**s, as well as **CysLT2 receptors** (Cysltr2), **histamine H_1 receptors** (HRH1), and **5-HT_{1F} receptors** (Htr1f) to transduce Il-31-, LTD_4-, histamine-, and 5-HT-mediated chronic allergic itch and inflammation (Abdelalim, Bellier, & Tooyama, 2016; Nguyen, Wu, Bonilla, von Buchholtz, & Ryba, 2017; Stantcheva et al., 2016; Usoskin et al., 2015; Table 2). Interestingly, **MrgprA3** is not detected in NP3 $Nppb^+$ neurons though both NP2 and 3 neurons are partially overlapping populations and express HRH1 as well as IL-33 receptors. These overlapping neurons also express other neuropeptides and neuropeptide receptors, including **somatostatin**, neurotensin, and neuropeptide Y. In another study, using flow cytometry in mice models, *Nppb* was demonstrated to be enriched in a distinct subpopulation with the low levels of Ret and absence of binding to plant isolectin B4, but these neurons express neuropeptides such as somatostatin, along with the NGF receptor, **tropomyosin receptor kinase**, and multiple transcripts associated with itch. The latter include Cysltr2, IL-31Rα, and oncostatin M receptor (Table 2). Furthermore, these neurons also express HRH1, Htr1A, Htr1f, **TRPM6**, **TRPV1**, and low levels of MrgprA3 (Stantcheva et al., 2016; Table 2). Interestingly, these neuronal population does not express MrgprC11, endothelin receptors, **thymic stromal lymphopoietin** receptor transcripts (*Il7r* and *Crlf2*), and **TRPA1** (Stantcheva et al., 2016). Recently the unique molecular programme associated with $Nppb^+$ NP3 neurons was shown to rely on the transcription factor Runx1, as development of NP3 neurons was impaired in Runx1 mutant mice and the impairment resulted in diminished acute and chronic itch response (Qi et al., 2017). Using in situ hybridization (ISH) in sections of human DRGs, the histamine receptor gene, HRH1, was largely co-expressed with *Nppb*, and all the $Nppb^+$ neurons express HRH1 (Qi et al., 2017). In human DRGs, the neurons positive for the antimalarial drug chloroquine receptor $(Mrgprx1)^+$ express *Nppb*, although some $Nppb^+$ cells are $Mrgprx1^-$. In addition, ISH also revealed that most of the human $Nppb^+$ neurons co-express *IL-31Rα* (Solinski et al., 2019; Table 2). These collective findings are consistent with the involvement of BNP in their agonists-induced itch behaviours (Mishra & Hoon, 2013; Pitake, Ralph, DeBrecht, & Mishra, 2018). Moreover, the itch responses to subcutaneously injected IL-31 were significantly attenuated in *Nppb*-KO mice and mice treated with

TABLE 1 Presence of BNP and its receptors in tissue, and phenotypes of their knockout in mice

Gene transcripts or protein	Expression	Consequence of knockout in mice
Nppb	Brain (Sudoh, Minamino, Kangawa, & Matsuo, 1988); kidney (Herten, Lenz, Gerzer, & Drummer, 1998); liver (Vollmar, Paumgartner, & Gerbes, 1997); thymus (Vollmar, Wolf, & Schulz, 1995); cardiac tissues (Kambayashi et al., 1990; Mukoyama et al., 1991); sensory ganglia (Goswami et al., 2014; Zhang et al., 2010); not expressed or tracelly expressed in dorsal spinal cord (Goswami et al., 2014; Wheeler, Lascelles, Olivry, & Mishra, 2019); gonadal adipose (Neinast et al., 2015); mucosal epithelium of terminal and respiratory bronchioles, smooth muscle cells in the lamina propria of terminal bronchioles and vascular smooth muscle cells, alveolar type II cells, and macrophages (Oztop et al., 2019; Vollmar et al., 1995); lens epithelial cells (Cammarata, Braun, Dimitrijevich, & Pack, 2010); Müller cells (Cao, Yu, Zhao, & Yang, 2004); retina (Fernandez-Durango, Nunez, & Brown, 1995; Rollin, Mediero, Roldan-Pallares, Fernandez-Cruz, & Fernandez-Durango, 2004); fat cells (Lafontan et al., 2005); pulmonary metastases (Margalit et al., 2003); proximal tubular cells (Mistry et al., 1998; Mistry et al., 2000)	*Nppb*$^{-/-}$ mice have vascular complications, and fibrosis (Holditch, Schreiber, Burnett, & Ikeda, 2016; Potter et al., 2009; Tamura et al., 2000). They also exhibit greatly attenuated responses to a range of pruritic agents (Mishra & Hoon, 2013; Mishra & Hoon, 2015)
NprA	Kidney, lung, adipose, adrenal, brain, eye, liver, heart, testis, and vascular smooth muscle tissue, thymus (Fernandez-Durango et al., 1995; Goy et al., 2001; Lowe et al., 1989; Nagase, Katafuchi, Hirose, & Fujita, 1997; Ohsaki, Gross, Le, Oie, & Johnson, 1999; Sarzani et al., 1999; Sekiguchi et al., 2001; Vollmar et al., 1997; Wilcox, Augustine, Goeddel, & Lowe, 1991); granulosa cells (De Cesaro et al., 2018); very low expressed in sensory ganglia (Goswami et al., 2014; Marchenkova et al., 2015; Vilotti et al., 2013; Zhang et al., 2010); gonadal adipose (Neinast et al., 2015); skeletal muscle (Coue et al., 2015); lens epithelial cells (Cammarata et al., 2010); NG108-15 (Muller, Hildebrand, Lubberstedt, Kuhn, & Middendorff, 2010); retina (Rollin et al., 2004); proximal tubular cells (Mistry et al., 2000; Noubani, Farookhi, & Gutkowska, 2000); decidua vera, chorion laeve, myometrium, and placenta (Itoh et al., 1994)	*NprA*$^{-/-}$ mice show high blood pressure, salt sensitivity, volume overload, and cardiac hypertrophy, fibrosis, and inflammation. (Kuhn et al., 2002; Lopez et al., 1995; Oliver et al., 1997; Pandey, 2019)
NprB	Bone, brain, fibroblasts, heart, kidney, liver, lung, uterine, and vascular smooth muscle tissue; eye (Bryan et al., 2006; Chrisman, Schulz, Potter, & Garbers, 1993; Dickey et al., 2007; Fernandez-Durango et al., 1995; Herman, Dolgas, Rucker, & Langub, 1996; Langub, Dolgas, Watson, & Herman, 1995; Sarzani et al., 1999; Vollmar et al., 1997); rat thymus (Vollmar et al., 1995); bovine granulosa cells (De Cesaro et al., 2018); sensory ganglia (Goswami et al., 2014; Mishra & Hoon, 2015); gonadal adipose tissue (Neinast et al., 2015); lens epithelial cells (Cammarata et al., 2010); retina (Rollin et al., 2004); proximal tubular cells (Mistry et al., 1998; Mistry et al., 2000); decidua vera, chorion laeve, myometrium, and placenta (Itoh et al., 1994)	*NprB*$^{-/-}$ mice have near-100% post-natal mortality, show dwarfism, seizures, female sterility, and decreased adiposity (Blaser et al., 2018; Pandey, 2019; Tamura et al., 2004)

(Continues)

TABLE 1 (Continued)

Gene transcripts or protein	Expression	Consequence of knockout in mice
NprC	Endothelial cells (Leitman et al., 1986); granulosa cells (De Cesaro et al., 2018); adrenal, brain, heart, kidney, liver, mesentery, eye, and vascular smooth muscle tissue (Fernandez-Durango et al., 1995; Nagase et al., 1997; Potter et al., 2006; Vollmar et al., 1997; Wilcox et al., 1991); thymus (Vollmar et al., 1995); DRG and TG (Goswami et al., 2014); white adipose tissue (Smith, Fahrenkrug, Jorgensen, Christoffersen, & Goetze, 2015); skeletal muscle (Coue et al., 2015); lens epithelial cells (Cammarata et al., 2010); α cells (Burgess et al., 2009); retina (Rollin et al., 2004); proximal tubular cells (Mistry et al., 2000); neonatal brain and in isolated primary cortical neurons (Ma & Zhang, 2018)	$NprC^{-/-}$ mice have a progressively reduced ability to concentrate urine, exhibit mild diuresis, and tend to be blood volume depleted, skeletal deformities associated with a considerable increase in bone turnover (Matsukawa et al., 1999; Pandey, 2019)

TABLE 2 Differential expression of BNP and its receptors in sensory ganglia and spinal cord

	Co-localized markers		
		Spinal cord	
Gene transcripts or protein	Sensory neurons	Dorsal horn	Ventral horn
Nppb	$TRPV1^+$ (Mishra & Hoon, 2013), $MrgprA3^+$ (Usoskin et al., 2015); $MrgprC11^+$ (Mishra & Hoon, 2013), PLCβ (Mishra & Hoon, 2013); $CGRP^+$ and $IB4^+$ neurons (Li et al., 2016); $Cysltr2^+$, $Htr1f^+$, and $S1pr1^+$ (Solinski, Kriegbaum, et al., 2019); somatostatin $(Sst)^+$ (Huang et al., 2018); NMB^+ (Mishra & Hoon, 2013); $Il31ra^+$, $S100b^+$, $Cpne6^+$ (Chiu et al., 2014; Li et al., 2016)	$CGRP^+$ (Abdelalim et al., 2016)	$CGRP^+$, $ChAT^+$ (Abdelalim et al., 2016)
NprA	$CGRP^+$ (Li et al., 2016)	Gastrin releasing peptide $(GRP)^+$ and Sst^+ (Chamessian et al., 2018; Kiguchi et al., 2016)	Unknown
NprB	Small and medium-sized $CGRP^+$, $IB4^+$ (Abdelalim, Bellier, & Tooyama, 2013); cGMP-dependent kinase-I $(cGKI)\alpha^+$ (Schmidt et al., 2007)	$CGRP^+$ (Abdelalim et al., 2013)	Unknown
NprC	Not expressed by DRG neurons but localized in cells—most likely Schwann cells or their precursors—associated with the dorsal roots of the spinal cord (Schmidt et al., 2016; Zhao & Ma, 2009)	Neuromedin B receptor $(NMBR)^+$ (Goswami et al., 2014)	Unknown

Nppb-saporin, a toxin that ablated 70% BNP receptor positive neurons in the spinal cord (Mishra & Hoon, 2013; Pitake et al., 2018). On the contrary, itch induced by intradermal injection of IL-31 in mice was not affected by intrathecal injection of Nppb-saporin and neurokinin B was selectively involved in IL-31-induced itch (Sakata et al., 2019). However, the percentage of the neuronal population ablated is lacking in this later study. A similar study is needed using *Nppb*-KO mice, to clarify this finding. Moreover, the RNA-sequence analysis for the overlapping subpopulations of $IL\text{-}31RA^+$ and neurokinin B^+ in sensory neurons has not been reported thus far (Chiu et al., 2014; Goswami et al., 2014; Li et al., 2016).

Apart from being the essential neuropeptide in sensory neurons, BNP has been detected in spinal cord motor neurons, and is co-localized with **CGRP** and **ChAT** in the ventral horn (Abdelalim et al., 2016). Moreover, NPRA was co-localized with $ChAT^+$ neurons in the brain stem (Abdelalim et al., 2016). Although BNP could play a role in the repair mechanisms following nerve injuries, the exact function of BNP in these neurons has not been established by experiments, so far.

4 | ROLE OF BNP IN ITCH TRANSMISSION IN THE SPINAL CORD

There are still debates about the involvement of the BNP located in the spinal cord, in pain or itch. In pain, BNP released from sensory neurons negatively regulates nociceptive transmission through its presynaptic GC receptor NPRA. This results in the activation of intracellular PKG and large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channel pathways in nociceptive neurons (Abdelalim et al., 2016; Zhang et al., 2010). A previous study showed that rather than generating pain, BNP inhibited the inflammatory pain through activation of NPRA which was expressed in CGRP-containing neurons, and the BNP as well as NPRA expression levels were increased after peripheral inflammation induced by intraplantar injection of formalin or Freund's complete adjuvant into the adult male rats (Zhang et al., 2010). Moreover, intrathecal injection of BNP inhibited formalin and Freund's complete adjuvant induced pain. Accordingly, intrathecal injection of BNP antibodies into these mice attenuated the recovery from pain (Zhang et al., 2010). Such inhibition of pain in the periphery by BNP was assumed to occur at the spinal cord level. However, these results conflicted with the later findings from Mishra's group showing that BNP-expressing sensory neurons were not involved in acute, inflammatory, or neuropathic pain, from results with *Nppb*-KO mice (Pitake et al., 2018).

The function of BNP as a mediator of itch was first described by Mishra and Hoon (2013). They identified BNP as an itch-specific neurotransmitter utilized by sensory neurons, and it was both necessary and sufficient to produce itch behaviour in mice. In their results obtained from *Nppb*-KO mice, BNP was necessary for both histaminergic and non-histaminergic itch and was expressed in a small number of TRPV1/MrgprA3/C11$^+$ unmyelinated C- and thinly myelinated Aδ-fibres of primary sensory nerve afferents. They also demonstrated BNP transmitted itch signals to NPRA expressed primarily in lamina I to contribute to spinal processing of itch (Mishra & Hoon, 2013). The BNP released from peripheral sensory neurons stimulates its receptor in NPRA$^+$-spinal cord neurons to release GRP in the spinal cord to activate canonical GRP receptor (*Grpr*)$^+$-neurons in order to transmit itch signal to the brain (Hoon, 2015; Kiguchi et al., 2016). In addition, *Nppb*$^{-/-}$ mice, but not *Grpr*$^{-/-}$ mice, exhibit scratching behaviour upon intrathecal injection of GRP (Mishra & Hoon, 2013; Sun & Chen, 2007).

Notably, it is still uncertain whether GRP is expressed and acts as a itch neurotransmitter in the sensory ganglia, because several studies were unable to detect its mRNA by ISH (Fleming, Kirby, & Penny, 2012; Mishra & Hoon, 2013; Wada, Way, Lebacq-Verheyden, & Battey, 1990) or RNA sequencing (Goswami et al., 2014; Usoskin et al., 2015), whereas others claimed it was expressed by primary sensory neurons (Barry et al., 2016). In contrast, GRP was detected predominantly in spinal cord neurons (Goswami et al., 2014; Usoskin et al., 2015). Thus, it is not clear if GRP-GRPR signalling plays a role in itch in the primary afferents (Liu et al., 2014). Nevertheless, it is possible that GRP expression levels are very low or non-existent.

To confirm that BNP is selective for itch, Mishra's group also used *Nppb*-KO mice in several pain models including chemically induced pain, inflammatory soup-induced pain, and nerve injury neuropathic pain and demonstrated that there is no any difference detected in perception of pain in these models (Pitake et al., 2018). Moreover, the *Nppb*$^+$ NP3 neurons co-express several itch-related receptors including MrgprA3$^+$, MrgprC11$^+$, PLC-ß, Cysltr^{2+}, Htr1f$^+$, S1pr1$^+$, Sst$^+$, and NMB$^+$ (Table 2).

Recent studies have shown that bile acids accumulated in the tissues of patients with cholestasis induced TRPA1 channel-dependent release of both GRP and BNP in the dorsal horn of the spinal cord in rats, implicating BNP in the profound pruritus associated with cholestatic disease. Furthermore, this study established that BNP is linked to the disease-relevant mechanism (Lieu et al., 2014). The significant contribution of spinal BNP to non-histaminergic itch was confirmed by Kusube et al., (2016), consistent with Mishra's finding that either elimination of BNP or the ablation of spinal interneurons expressing NPRA was enough to profoundly attenuate scratching responses to several pruritogens, including chloroquine, 5-HT and compound 48/80 in mice (Mishra & Hoon, 2013).

In human psychophysical studies, most chemical-induced itch sensations are accompanied by weaker nociceptive sensations, such as burning, pricking or stinging (LaMotte, Dong, & Ringkamp, 2014; Liu et al., 2012; Sikand, Dong, & LaMotte, 2011; Sikand, Shimada, Green, & LaMotte, 2009). This raises an interesting question whether BNP is also involved in pain generation in humans. These mixed sensations also question the "selectivity" of itch pathways (Sun et al., 2017). Thus, an elegant study concluded that *Grp*$^+$-neurons positively code for itch while negatively regulating pain transmission with a "leaky gate" (Sun, Xu, et al., 2017). In addition, substance P (encoded by *Tac1* gene) has been identified as the transmitter used by *Grpr*$^+$ neurons in the activation of the last step in the spinal cord itch circuit and the stimulation of spinothalamic projection interneurons (Sakai et al., 2016). There are several studies on BNP in induction of the delayed modulation of TRPV1 channels and P2X3 receptors in mouse TGNs (Marchenkova, van den Maagdenberg, & Nistri, 2016; Marchenkova, Vilotti, Fabbretti, & Nistri, 2015; Marchenkova, Vilotti, Ntamati, van den Maagdenberg, & Nistri, 2016; Vilotti, Marchenkova, Ntamati, & Nistri, 2013). But these studies lack further linkage of this function with the involvement of BNP in diseases. In-depth investigations are needed to investigate if BNP is involved in potentiation of these channel proteins to enhance the itch sensitization. It alsonot clear how the BNP-dependent P2X3 receptor modulation are initiated in trigeminal neurons because NPRA barely exists in sensory neurons (Table 2).

At the spinal cord level, scratching behaviour was significantly diminished upon intrathecal injection of either BNP or GRP in *R7bp* KO mice, suggesting that the BNP-GRP pathway is dependent on the $Ga_{i/o}$-directed GAP activity in sensory systems (Pandey et al., 2017). The inhibitory spinal $GABA_A$ receptors mainly contain α1, α2, α3, or α5 subunits together with β2/3 subunits and a γ subunit. The antipruritic action of TPA023B, a selective ligand of the pentameric channel α2/α3$GABA_A$ receptor, has been demonstrated to reduce

scratching behaviours in the acute model elicited by intrathecal injection of BNP or GRP and the chronic oxazolone models in mice, as well as HDM-induced atopic dermatitis (AD) model in dogs (Ralvenius et al., 2018). This finding is consistent with an itch inhibitory effect occurring primarily via intrinsic dorsal horn neurons, involving GABA pathways in BNP-GRP itch transmission (Ralvenius et al., 2018; Figure 1). It is also in agreement with the notion that pain neurons and touch neurons can inhibit ascending itch signals via GABAergic interneurons (Steinhoff, Oaklander, Szabo, Stander, & Schmelz, 2019; Steinhoff, Schmelz, Szabo, & Oaklander, 2018). In relation to the touch-induced inhibition of both pain and itch, it would also be interesting to investigate if excitation of glycinergic inhibitory neurons in the spinal dorsal horn could also reduce itch inhibition by targeting postsynaptic BNP pathways.

5 | PERIPHERAL ROLE OF BNP IN ITCHY SKIN

Nppb$^+$ NP3 neurons innervate the border area between dermis and epidermis in both hairy and glabrous skin (Stantcheva et al., 2016), and NPRA and NPRB are expressed in both epidermis and dermis (Meng et al., 2018). In the periphery, somatostatin is exclusively expressed in *Nppb*$^+$ neurons (Table 2). In these neurons, somatostatin potentiates itch by inhibiting inhibitory dynorphin subset B5-I neurons, and this results in disinhibition of *Grpr*$^+$-neurons (Huang et al., 2018). Recently, our group found that BNP is also expressed in chronic pruritic AD skin and its innervated sensory neurons (Meng et al., 2018). Additionally, the signal from immuno-reactive BNP is enhanced in skin from AD patients or from HDM-treated mice (Meng et al., 2018; Figure 1). Likewise, levels of BNP in the skin were increased in animal models of itch (Ewald et al., 2017; Liu et al., 2016; Meng et al., 2018), as well as in diseased skins with AD (Meng et al., 2018; Figure 2a) or psoriatic conditions (Meng et al., 2018; Nattkemper et al., 2018). We also observed that BNP level was increased in human prurigo nodularis skin (Figure 2a). All of these findings implicated BNP in persistent itch in skin, although peripheral injection of BNP is unable to elicit itch behaviours in mice (Mishra & Hoon, 2013).

We have shown that BNP is an essential messenger molecule for Th2 cell-mediated itch transduction in skin (Meng et al., 2018). In primary human keratinocytes (phKCs), several key intracellular phospho-

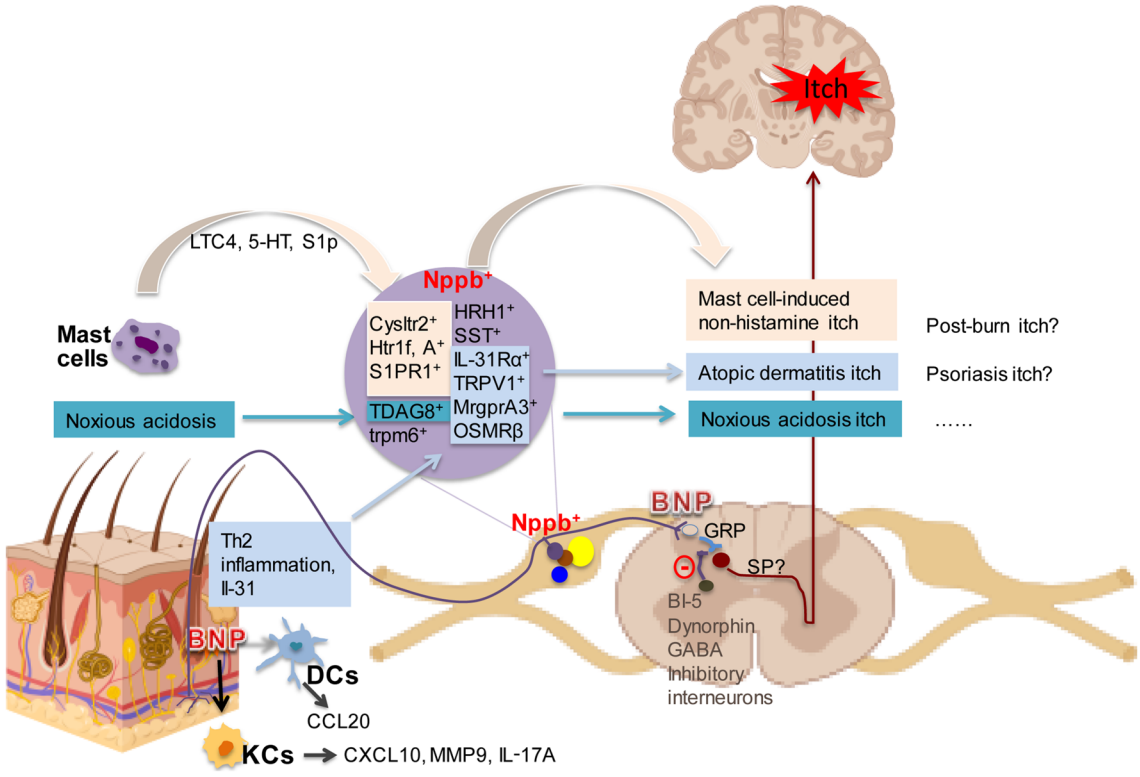

FIGURE 1 BNP plays critical roles in itch transmission. Mast cell activation elicits the release of LTC_4, 5-HT, and S1P. These mediators subsequently bind to their respective receptors expressed in *Nppb*$^+$-sensory neurons. Noxious acidosis activates TDAG8 in *Nppb*$^+$ neurons. Th2 inflammation results in IL-31 release which activates sensory neurons to release BNP. The elevated BNP level in skin promotes the release from KCs and dendritic cells of several inflammatory and pruritic cytokines including CCL20, CXCL10, IL-17A, and MMP9 (as indicated). Activation of *Nppb*$^+$-sensory neurons also results in BNP release at their central terminals, followed by binding to GRP$^+$ spinal cord neurons. This BNP-GRP itch pathway is under the regulation by BI-5, dynorphin, and GABA releasing inhibitory interneurons. In addition, inhibition of BNP receptors by antagonists or inducing $GABA_A$ receptor expression on GRP neurons can lead to block of the pruritus. [Colour figure can be viewed at wileyonlinelibrary.com]

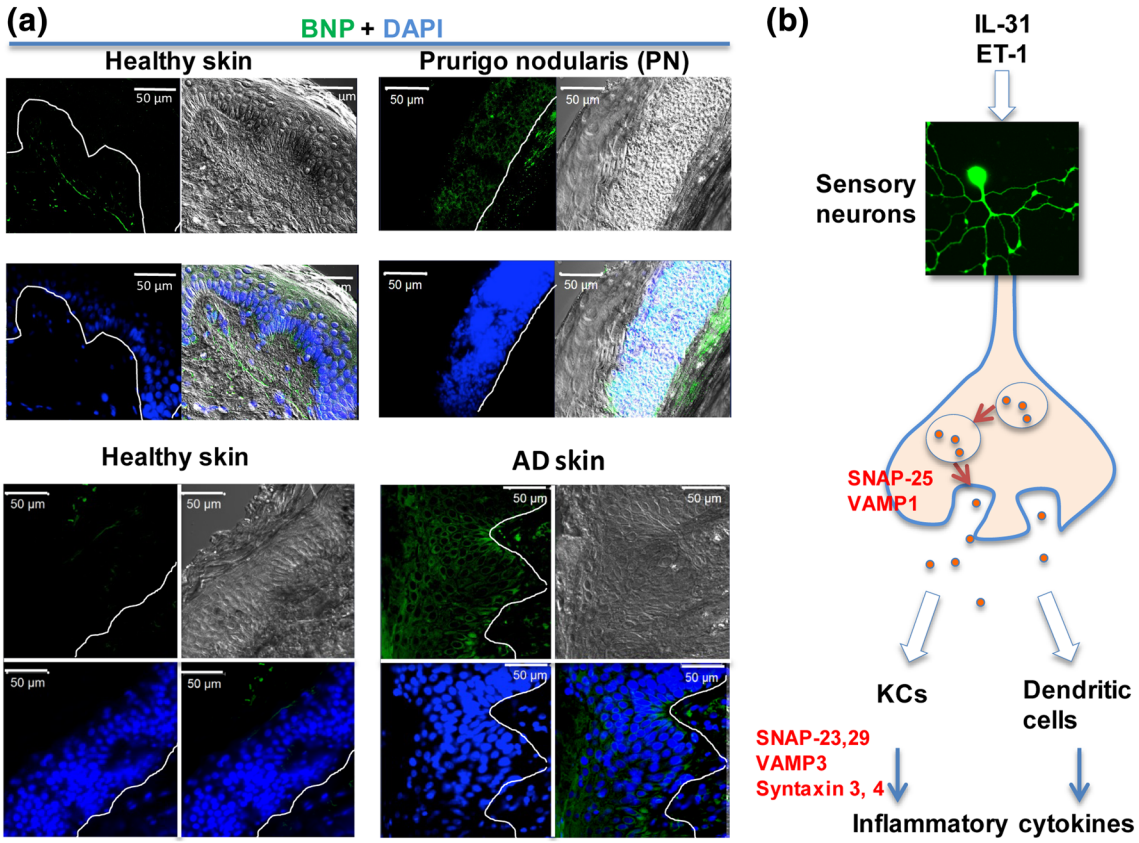

FIGURE 2 BNP immuno-reactive signals are increased in human itchy skin and its release from sensory neurons is via a SNARE-dependent mechanism. (a) Skin BNP is up-regulated in itchy human skin, including AD and prurigo nodularis (PN); green, BNP; and blue, DAPI. (b) IL-31- and ET-1-induced BNP release from sensory neurons is through SNARE-dependent mechanisms. In addition, different isoforms of SNARE proteins are also required by BNP-induced pruritic and inflammatory cytokine release from phKCs, including ET-1. The latter can further stimulate BNP release from sensory neurons. Thus, it might result in amplification of itch circuits. Immunohistochemistry was performed as in Meng et al. (2018). All the clinical samples were purchased from Tissue Solutions Ltd (Glasgow) [Colour figure can be viewed at wileyonlinelibrary.com]

kinases were activated by BNP, and this elicited several cytokines (Figure 2b), involved in itchy skin (Meng et al., 2018). The effect of BNP in skin cells is closely correlated with dermatological diseases and conditions (Meng, Wang, Buddenkotte, Buhl, & Steinhoff, 2019). To reveal the connections between the shared differentially regulated genes (Figure 3a), we constructed the biomolecular networks in BNP-activated phKCs (Figure 3b), and the established and putative interactions of cytokines were shown using IPA analysis (Figure 3b). The differentially regulated genes were associated with one another directly or indirectly. Validating these signalling pathways may aid in identification of biomarkers for chronic itch or potential therapeutic targets.

Within AD, different TRP channels constitute a large family of ion channels activated in response to distinct itch stimuli at skin, peripheral, and central sensory neuronal levels. Importantly, BNP was demonstrated by ISH to be expressed in a fraction of both mouse and human *TRPV1*$^{+}$-neurons (Solinski, Dranchak, et al., 2019). **IL-31** and **endothelin 1** (ET-1) released from Th2 cells initiate a closed itch circuit between sensory neurons and skin cells, as well as immune cells, through BNP. Thus, BNP acts as an itch relay centre (Meng et al., 2018; Meng et al., 2019). In addition, BNP further augments AD-related cytokine release from skin cells, through its specific receptors elevated or activated in diseased epidermal skin. Notably, **toll-like receptor**s mediate ET-1 release from keratinocytes, which might activate DRGs, leading to the release of BNP. In this scheme, the toll-like receptor represents an "innate biosensor" to bridge skin and central itch (Szollosi et al., 2019). Thus, BNP plays a bidirectional part on intercellular networks to initiate itch at the level of the spinal cord and simultaneously to amplify itch-related inflammatory signals in peripheral skin.

Although BNP is known to be the key molecule in Th2-initiated itch circuits in AD through IL-31-regulated mechanisms, it is not known if BNP could modulate TRP, the non-selective cation channels, in the sensory neurons and the skin to contribute to itch, even though *Nppb*$^{+}$ and *MrgprA3*$^{+}$ neuronal cells co-express the TRPV1 (Liu et al., 2009; Mishra & Hoon, 2013) and TRPA1 channels (Lieu et al., 2014). The TRPV1 channels respond to many different noxious stimuli and were involved in IL-31-mediated itch in mice (Cevikbas et al., 2014). Thus BNP modulation of TRPV1 channels might underlie hypersensitivity to noxious stimulation in neurogenic inflammation.

Another significant role for BNP in skin-derived itch is likely because *Nppb*$^{+}$-neurons are the sensors of mast cell-induced itch

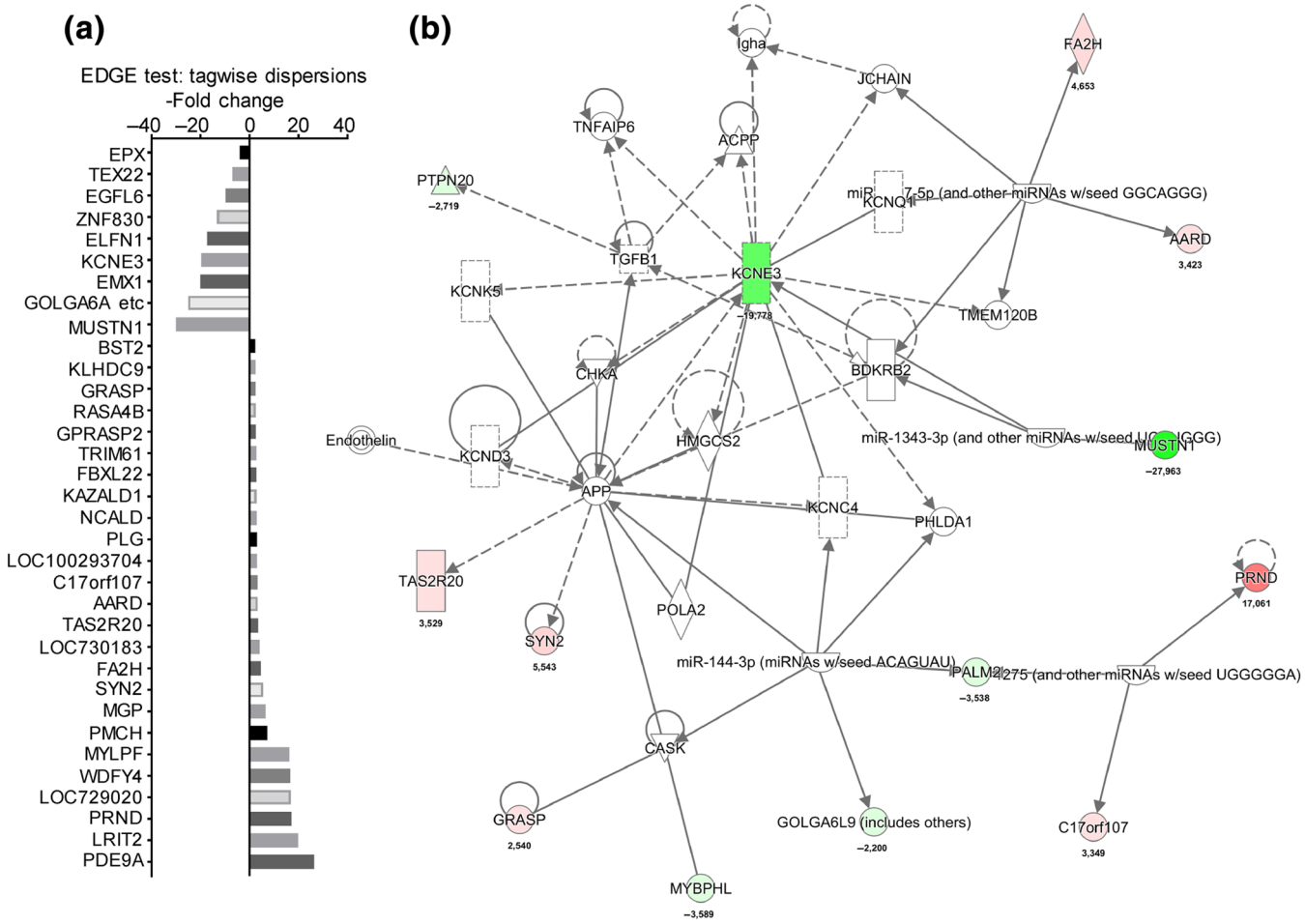

FIGURE 3 Transcriptome analysis of BNP-treated phKCs showed changes of gene transcriptions which generated de novo discovery of pathways in phKCs. (a) Genes affected by BNP in phKCs. (b) Highly interconnected networks illustrate the relationship between the regulated gene profiles identified by RNAseq from BNP-treated phKCs. Hot and cold coloured genes are up- and down-regulated respectively. Transcriptome experiments and analysis was carried as described in Meng et al. (2019). IPA analysis was performed using QIAGEN's Ingenuity Pathway Analysis (QIAGEN Bioinformatics) software [Colour figure can be viewed at wileyonlinelibrary.com]

(Figure 1). Skin-resident mast cells are key players in the histamine-dependent, type 1 hypersensitivity itch. Mast cells also release 5-HT, LTC_4, and **sphingosine-1 phosphate** (S1P) to induce scratch responses via GRP signalling in spinal cord. Interestingly, these non-histamine pruriception from mast cells are dependent on *Nppb*$^+$-sensory neurons activation because 5-HT_{1F}, $CysLT_2$ and **S1P receptors** were expressed in *Nppb*$^+$-neurons (Solinski et al., 2019). In addition, noxious acidosis-induced itch upon intradermal injection into mice, also activates *Nppb*$^+$-sensory neurons via a TRPV1 channel-dependent mechanism, and the proton-sensing GPCR, **TDAG8 (GPR65)**, is highly expressed on *Nppb*$^+$-neurons (Lin et al., 2017; Figure 1).

6 | POTENTIAL THERAPEUTIC TARGETS FOR BNP SIGNALLING IN ITCH

Insight into the functionality of BNP in modulation of itch signal transmission, pruritic channel function, and mediating the release of itch mediators certainly aids in developing novel effective therapies to treat this debilitating and widespread condition. As a result, targeting BNP signalling is a logical approach to new therapeutic agents. Although BNP signalling has been effectively targeted in animal models of acute and chronic itch, there is still a long way to go for clinically useful compounds.

Thus far, many antagonists have been synthesized to inhibit the BNP signalling pathway. These classic pharmacological inhibitors against BNP signalling include **HS-142-1**, **anantin** and **A71915**. HS-142-1 is a potent non-peptide microbial polysaccharide antagonizing natriuretic peptide receptors (Morishita et al., 1991) and anantin is an NPR antagonist extracted from fungi to reduce the increase of intracellular cGMP produced by ANP or BNP (Wyss, Lahm, Manneberg, & Labhardt, 1991). A71915 is a synthetic derivative of ANP and can inhibit NPRA competitively (Delporte, Winand, Poloczek, Von Geldern, & Christophe, 1992). Among them, only A71915 has been tested for itch relief in animal models (Solinski, Dranchak, et al., 2019).

6.1 | Current achievement in targeting BNP signalling for itch relief

Initially, Kiguchi et al. observed that the onset and magnitude of intrathecal BNP-induced scratching are slower and smaller than that induced by intrathecal GRP (Kiguchi et al., 2016), thus raising the hypothesis that BNP initiates itch indirectly through activation of a GRP pathway. They showed that intrathecal administration of BNP antagonist A71915 in mice had no effect on intrathecal GRP-induced scratching, whereas the GRP antagonist **RC-3095** inhibited BNP-induced scratching (Kiguchi et al., 2016), confirming that the BNP-NPRA system may act upstream of GRP-GRPR to regulate itch in the mouse spinal cord (Kiguchi et al., 2016). In their study, A71915 also had little effect on peripherally elicited scratching upon intradermal injection of ET-1, thromboxane A_2 analogue, **BAM8-22** (activator of MrgprC11), and **SLIGRL** (a **PAR2** agonist) in mice, thus concluding that there was a minimal role for the spinal BNP-NPRA system in regulating peripheral itch (Kiguchi et al., 2016). Their finding was later challenged by Mishra & Hoon (2013), who found that elimination of *Nppb* or the ablation of spinal interneurons expressing NPRA profoundly attenuated scratching response to intradermal administration of histamine, chloroquine, ET-1, 5-HT, SLIGRL, and compound 48/80. Quite recently, the effectiveness of A71915 in blocking NPRA activity by competing for binding sites with BNP, was re-examined. They showed that A71915, in fact, acts partly as a strong agonist at NPRA (Solinski, Dranchak, et al., 2019). Further high-throughput screening on a stable cGMP sensory cell line expressing human NPRA and NPRB to screen the candidate molecules from a large chemical library, identified a specific antagonist JS-11 and two other promising ligands for human NPRA and NPRB (Solinski, Dranchak, et al., 2019). Upon intraperitoneal or intrathecal administration, JS-11 was effective in eliminating pruritic behaviours in acute and contact dermatitis mice models as well as relief of IL-31-dependent hapten-induced itch, but not skin inflammation, in mice (Solinski, Dranchak, et al., 2019). This is a breakthrough finding that has great potential in finding a direct inhibitor for the BNP-NPR pathways, with good prospects for alleviating itch. However, as rightly recognised by the authors, new compounds such as JS-11 still have limitations because of relatively low affinities, cross-reactivities, possible side effects and inadequate physiocochemical properties.

6.2 | Antibody targeting of BNP pathways

BNP can be used as diagnostic and prognostic marker for patients with heart failure. It is noteworthy that so far the screening of anti-BNP single-chain variable fragment (scFv) from phage display, and its production in Escherichia coli or in methylotrophic yeast Pichia pastoris, have been successful (Bu, Zhou, Tang, Jing, & Zhang, 2013; Maeng, Choi, Sa, Shin, & Kim, 2012; Maeng, Nam, & Kim, 2011; Zhang, 2013). However, these antibodies have not yet been used as therapeutic agents to inhibit BNP-NPRA signalling, despite being highly specific. Most of them were designed to measure BNP levels in the analytical diagnosis of heart failure, with the advantage of their small size compared with that of the whole antibody.

Most recently, a therapeutically relevant, intact full-length anti-NPRA IgG4-humanized monoclonal antibody has been created and identified to specifically target the NPRA extracellular domain bound to its natural cyclic natriuretic peptide ligands (Blech et al., 2019). However, this antibody was created to stabilize the receptor-peptide complex and potentiate BNP-dependent cGMP production in NPRA-presenting HEK cells.

It might be worthwhile to develop the functional anti-BNP ScFv, or the full length antibody, to reduce levels of BNP in skin or to antagonize the biological action of NPRA by interrupting the BNP-NPRA binding, in order to interfere with itch transmission.

6.3 | Targeting exocytotic proteins involved in BNP release

For targeting purposes, one of the interesting findings is that the synthesis and release of BNP from pruritic sensory neurons differ from other neurotransmitters, such as **substance P** and CGRP. Release of BNP could be elicited by IL-31 (Meng et al., 2019; Pitake et al., 2018) and ET-1 (Meng et al., 2019), the key itch mediators that play important roles in the pathogenesis of AD. In contrast, IL-31 did not elicit synthesis and release of CGRP or substance P. The enhanced BNP release, but not its resting level, from pruritic sensory neurons requires a particular exocytotic process involving the soluble N-ethylmaleimide-sensitive factor activating protein receptor (SNARE) (Meng & Wang, 2015). We found that vesicle-associated membrane protein 1 (VAMP1) and synaptosome-associated protein 25 kDa (SNAP-25), but not VAMP7, mediated BNP release (Meng et al., 2018). These exocytotic proteins might serve as promising targets for blocking BNP-mediated itch (Figure 2b). In addition, different SNARE isoforms also regulate the release of ET-1, thymic stromal lymphopoietin, and many other itch-related cytokine/chemokines, from skin cells that play important roles in immune-neuron communication (Meng et al., 2019; Figure 2b). Thus, targeting these SNARE proteins should break the crosstalk link between sensory neurons and skin cells. In this perspective, SNARE-inactivating agents, such as botulinum neurotoxins, have shown promising in certain itchy diseases which include lichen simplex chronicus, psoriasis and rosacea, meralgia paresthetica, and post-burn (Akhtar & Brooks, 2012; Boozalis, Sheu, Selph, & Kwatra, 2018; Heckmann, Heyer, Brunner, & Plewig, 2002; Perez-Perez et al., 2014; Salardini, Richardson, & Jabbari, 2008; Wallengren & Bartosik, 2010; Weinfeld, 2007; Zanchi et al., 2008). Altogether, these findings highlight the importance of SNARE as a therapeutic target in the treatment of chronic itch diseases.

6.4 | Targeting BNP-activated intracellular kinases

Intracellular kinases including **p38**, **ERK1/2**, **JNK**, and **glycogen synthase kinase 3,** activated by BNP in phKCs, might also be potential

targets (Meng et al., 2018). Upon their activation, BNP induced release of CXCL10, MMP9, and IL-17A. Inhibition of glycogen synthase kinase 3 abolished IL-17A release. IL-17A is a critical cytokine implicated in itchy atopic and psoriatic skin where it feeds back to KCs to activate further inflammatory response. In addition, BNP also activated c-Jun in cultured human dendritic cells, and meantime, it induced CCL20 release. This neuron-immuno-modulatory mechanism might result in the activation of immature dendritic cells, which could contribute to the persistent itch (Meng et al., 2019). Selective inhibition of these kinases might benefit the recovery of itch and its associated inflammatory skin conditions. As these intracellular kinases are also needed by other cell types or tissues, local application of these inhibitors is necessary to avoid the potential side effects.

6.5 | Targeting upstream regulators of BNP

In phKCs, BNP also induced transcription changes of many other genes including WD repeat- and FYVE domain-containing protein 4 (Meng et al., 2019; Figure 3a). Some of these genes were shown be linked to certain types of skin diseases, for example, WD repeat- and FYVE domain-containing protein 4 is known to be associated with the autoimmune disease, systemic lupus erythematosus (Yang et al., 2010; Zhang, Bo, Zhang, Zhuang, & Liu, 2014). Further validation of these genes might identify molecules that are pivotal in regulating BNP signalling. Importantly, in relation to the predicted BNP-induced network in phKCs (Figure 3b), their upstream regulators might include key itch mediators such as IL-27 and plasminogen activator, urokinase (PLAU) or receptor (PLAUR), or endothelin receptor (Table 3). These upstream regulators need to be validated before being considered as potential targets for BNP-mediated itch signalling.

7 | FUTURE DIRECTIONS

The recent advances in our understanding of the molecular mechanism of BNP action in itch communication between immune cells, sensory neurons, and spinal cord central neurons highlight its importance as a therapeutic target to block itch transmission. It facilitates drug development with biomarkers of chronic itch across a range of skin diseases. Future studies will focus on evaluating the utility of BNP as the biomarker for chronic itch diagnosis and evaluation of

TABLE 3 BNP-induced transcription changes in phKCs predicted the upstream regulators that might serve as potential targets for blocking BNP-mediated, skin-derived, itch signalling

Top upstream regulators	Molecule type	Activation *z*-score	*P* value of overlap	Target molecules in dataset
miR-1254 (and other miRNAs w/seed GCCUGGA)	Mature microrna	1,122	1,61E-03	EMX1, PTPN20, TAS2R20, TEX22
IL27	Cytokine		1,70E-03	BST2, LAG3, TNFSF13
SNAP91	Other		1,85E-03	BST2
PLAUR	Transmembrane receptor		2,02E-03	C5AR1, PLG
miR-296-5p (miRNAs w/seed GGGCCCC)	Mature microrna	−0,020	2,36E-03	BMP8A, GRASP, KAZALD1, NCALD, TEX22, TNFSF13
miR-4515 (miRNAs w/seed GGACUGG)	Mature microrna		2,73E-03	EMX1, GOLGA6L9 (includes others), LAG3
KCNE2	Ion channel		3,69E-03	KCNE3
miR-4660 (miRNAs w/seed GCAGCUC)	Mature microrna		5,50E-03	GOLGA6A (includes others), NCALD, SYN2
INPP1	Phosphatase		5,53E-03	MYLPF
EPZ004777	Chemical reagent		5,53E-03	HOXA10
DNM2	Enzyme		5,53E-03	BST2
Lanthanum chloride	Chemical reagent		5,53E-03	MGP
PLAU	Peptidase		6,43E-03	C5AR1, PLG
Endothelin receptor	Group		7,36E-03	MYLPF
RGL2	Other		7,36E-03	MYLPF
miR-4661-3p (and other miRNAs w/seed AGGAUCC)	Mature microrna		8,48E-03	AARD, BMP8A
CCL15	Cytokine		9,20E-03	EPX
miR-1299 (miRNAs w/seed UCUGGAA)	Mature microrna		1,05E-02	GOLGA6A (includes others), NCALD
CAMP	Other		1,05E-02	BMP8A, C5AR1
AP2M1	Transporter		1,10E-02	BST2

Note. The presented deep-sequence data have been published (Meng et al., 2019) and are re-analysed here by post-informatics (Dong, Wu, Li, Wu, & Wang, 2018; Sun et al., 2017; Wang et al., 2015; Zhang et al., 2017).

effectiveness of targeted therapeutics; investigate if any of the established antagonists, such as HS-142-1 or anantin, would act as itch relief agents; and create antibodies interrupting BNP-NPRA pathways. Moreover, experiments will also involve the confirmation of lack of side effects on other tissues expressing NPRA, including the kidney and the vasculature (Potter, Abbey-Hosch, & Dickey, 2006). For example, it would be worth investigating if interfering with BNP signalling or NPRA pathways might have effects on blood pressure and hypertension, sodium excretion, vascular complication, salt sensitivity, volume overload, and cardiac hypertrophy, inflammation, and fibrosis, as described and observed in mice after ablation of BNP or NPRA (Table 1).

Considering that the BNP-NPRA itch signalling pathway is conserved between mice and humans, defining JS-11 or developing other more potent and selective NPRA antagonists would be beneficial in relief of itch in humans. Such relief would be valuable in a range of conditions including AD, cholestatic liver disease, opioid therapy and also nervous system disorders (e.g., multiple sclerosis), as well as infection and end stage kidney disease (Lieu et al., 2014). Although BNP has only recently been discovered, inhibition of its signalling pathways provides a real prospect for the treatment of chronic itch, a condition that is mostly resistant to treatment with traditional medicines. There is a real need for newly designed inhibitors for NPRA, for patient-reported outcomes and for clinical assessments.

7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander, Christopoulos et al., 2019; Alexander, Fabbro et al., 2019a; Alexander, Fabbro et al., 2019b; Alexander, Mathie et al., 2019).

ACKNOWLEDGEMENTS

The authors' research that is relevant for this review is and has been supported by Science Foundation Ireland (SFI) Investigators' Awards: Grant 15/SIRG/3508T to J.M. and Grants 13/CDA/2093 and 17/TIDA/4977 to J.W.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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How to cite this article: Meng J, Chen W, Wang J. Interventions in the B-type natriuretic peptide signalling pathway as a means of controlling chronic itch. *Br J Pharmacol*. 2020;177:1025–1040. https://doi.org/10.1111/bph.14952