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Research paper

Effects of potassium channel modulators on the responses of mammalian slowly adapting mechanoreceptors

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ABSTRACT

Introduction: slowly adapting mechanoreceptors in the skin provide vital tactile information to animals. The ionic channels that underlie their functioning is the subject of intense research. Previous work suggests that potassium channels may play particular roles in the activation and firing of these mechanoreceptors.
Objective: We used a range of potassium channel blockers and openers to observe their effects on different phases of mechanoreceptor responses.
Methods: Extracellular recording of neural activity of slowly adapting mechanoreceptors was carried out in an in vitro preparation of the sinus hair follicles taken from rat whisker pads. A range of potassium (K^+) channel modulators were tested on these mechanoreceptor responses. The channel blockers tested were: tetraethylammonium (TEA), barium chloride ($BaCl_2$), dequalinium, 4-aminopyridine (4-AP), paxilline, XE 991, apamin, and charybdotoxin.
Results: Except for charybdotoxin and apamin, these drugs increased the activity of both types of slowly adapting units, St I and St II. Generally, both spontaneous and evoked (dynamic and static) activities increased. The channel opener NS1619 was also tested. NS1619 clearly decreased evoked activity (both dynamic and static) while leaving spontaneous activity relatively unaffected, with no clear discrimination of effects on the two types of St receptor
Conclusion: These findings are consistent with the targets of the drugs suggesting that K^+ channels play an important role in the maintenance of spontaneous firing and in the production of and persistence of mechanoreceptor activity.

Introduction

In the vertebrate skin, low threshold mechanoreceptors can be broadly categorized into two classes depending on their responses to tactile stimuli: rapidly adapting and slowly adapting. Slowly adapting (SA) mechanoreceptors are distinguished by their sustained response to static mechanical stimuli. According to the pattern of firing that can be recorded from their afferent nerve fibres, they can be further categorized into SA I and SA II (or St I and II in sinus hairs). Studies in primates, including humans, indicate that slowly adapting type SA I mechanoreceptors (associated with Merkel cell neurite complexes), are responsible for high resolution pattern discrimination by the fingertips (Vallbo and Johansson, 1984, Johnson, 2001). The highest concentration of Merkel cell neurite complexes in rodents is found in sinus hairs (Halata et al., 2003). Merkel cell neurite complexes are also found in human hair follicles (Mahrle and Orfanos, 1974). Prominent sinus hairs, present in many animals, are essential tactile organs used to sense the immediate environment: for hunting, food foraging (Dehnhardt et al., 2003, Anjum et al., 2006) and for spatial navigation (LaMendola and Bever, 1997). Behavioural studies have shown that the rat's vibrissa system has a discriminative ability comparable to primate fingertips (Carvell and Simons, 1990). As in primate fingertips, St I mechanoreceptors in the sinus hair follicle complex are likely to play a major role in the highly developed discriminative abilities of rodents and other whisker-bearing animals. SA II mechanoreceptors are more uniformly distributed in the skin than SA I, and are not highly concentrated in primate fingertips.

Currently, there is enormous interest in identifying the roles that specific ion channels play in mechanotransduction processes (Lumpkin

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et al., 2010, Jin et al. 2020, Joshi et al., 2021). In the case of Merkel cell neurite complexes, there appear to be several possible ion channel candidates worthy of consideration. One area of research that has received surprisingly little attention is the role of potassium ion (K^+) channels in mechanotransduction. Potassium channels determine the resting membrane potential of many types of cells and control the excitability and spike frequency adaptation of neurones. K^+ channel opening leads to hyperpolarization of the cell membrane, resulting in a decrease in cell excitability. The natural plant alkylamide sanshool evokes tingling paraesthesia which has been attributed to an action at two-pore K^+ channels (Lennertz et al., 2010). However, comparison among different mechanoreceptor types indicates that only those with higher mechanical thresholds (> 5 mN, therefore not SA I or SA II) show increased firing to sanshool (Lennertz et al., 2010). Previous electrophysiological studies demonstrated the presence of K^+ currents in isolated Merkel cells (Yamashita et al., 1992) who reported two types of K^+ current: a 4-aminopyridine (4-AP) sensitive transient I_A type current and a sustained current which was resistant to 4-AP but blocked by both TEA and quinacrine. Merkel cells express the I_A type voltage-gated K^+ channel subunits KV4.2 and KV1.4, and modifier/silencer KV8.1. Significantly they also express the calcium-sensitive large-conductance K^+ channel BK (aka KCa1.1, SLO-1, Maxi-K^+, KCNMA1) subunit (Haeberle et al. 2004, Piskorowski et al., 2008). BK channels are ubiquitous at presynaptic endings of various neurones, and co-localize with voltage-gated calcium channels at transmitter release sites (Robitaille et al., 1993). We and others have discovered the same vesicle release machinery in Merkel cells as neurons (Haeberle et al., 2004, Hitchcock et al., 2004). The functional coupling between BK and Ca^{2+} channels could serve to regulate neurotransmitter release. BK channel blockade has been shown to both increase (Wang et al., 2001) and decrease (Skinner et al., 2003) synaptic release, depending on the particular presynaptic dynamics. There is good evidence for neurotransmission from Merkel cell to the nerve ending (Fagan and Cahusac, 2001, Fechner and Goodman, 2018, Hoffman et al., 2018, Higashikawa et al., 2019).

The sensitivity of both St I and St II units to low concentrations of TEA suggests that large Ca^{2+}-activated K^+ channels may not be involved (Lancaster, 1991). It will be of interest to further pharmacologically characterize the K^+ channels involved in St I mechanotransduction, contrasting the drug effects with that seen in St II units. This study examines the effects of selective K^+ channel blockers/activators to determine the functional contributions of different channels to the response and spontaneous firing characteristics of the two types of SA mechanoreceptors.

Understanding the basic mechanisms of low-threshold mechanoreceptors may also provide insights into the clinical management of pathological pain. For example, mechanical allodynia is triggered by low threshold mechanoreceptors (Lolignier et al., 2015, Chamessian et al., 2019). Functional information about Merkel cells may provide insights necessary for the future clinical treatments of the Merkel cell carcinoma (Xue and Thakuria, 2019), a particularly aggressive tumour associated with excess exposure of the skin to ultraviolet light (sunlight).

Methods

All procedures complied with the European Directive 86/609/EEC and royal decree no. 7/B/9512 dated 18/5/1422 H for the National Committee of Bioethics, Saudi Arabia. Ethical permission for the experiments were granted by Psychology Department Ethics committee of Stirling University and by the King Faisal Specialist Hospital and Alfaisal University IRB (# 2013–022).

Forty male Wistar-derived and Sprague-Dawley rats, with a mean weight of 423 g were used in these experiments. Animals were killed either by anaesthesia (2 g/kg) followed by intracardial urethane or by carbon dioxide. Whisker pads were removed and placed in cooled carbogenated (medical 95% and 5% carbon dioxide) synthetic interstitial fluid (SIF). Sinus hairs with follicles and 7 mm length of the deep vibrissal nerve were micro dissected as previously described (Cahusac and Mavulati, 2009, Cahusac and Senok, 2020). A selected sinus hair was then slit open lengthwise, cleared of blood, and mounted in a custom-made organ bath (courtesy of Professor Klaus Baumann, Hamburg)(Baumann et al., 1996). The slit was then pinned open using stainless steel insect pins to facilitate access of carbogenated SIF and drugs. The preparation was submerged in SIF except for the end of the deep vibrissal nerve, which was attached to a silver recording wire submerged below the SIF in fluorinert (FC-40 Sigma, Poole, UK). This allowed electrical isolation yet oxygenation of the recorded section of the vibrissal nerve. Bath temperature was maintained between 29 and 33 °C, and within ± 1 °C for a given experiment, since temperature fluctuations can have large effects on the activity of slowly adapting mechanoreceptors (Cahusac and Noyce, 2007). Fresh SIF was prepared using the following: NaCl (107.80 mM), sucrose (7.60 mM), $NaHCO_3$ (26.19 mM), D-gluconic acid (9.63 mM), D-glucose (5.55 mM), KCl (3.49 mM), $NaH_2PO_4 0.2\ H_2O$ (1.88 mM), $MgSO_4 0.7\ H_2O$ (0.69 mM) and $CaCl_2$ dihydrate (1.90 mM) (Bretag, 1969). This SIF was continuously carbonated throughout the experiment, flowing into the bath and removed at a rate of 1 ml/minute.

The hair shaft was trimmed to approximately 5 mm, and a piezo stimulator attached to allow mechanical deflection. The nerve sheath was removed from the nerve. The exposed nerve was then split and small bundles of nerves isolated for recording by attachment to the submerged silver wire. Electrical activity of single mechanoreceptor units was recorded from the nerves, see Figs. 4 and 5 insets, using Digitimer NeuroLog equipment (Welwyn Garden City, UK). Viable units were searched for by deflecting the hair shaft with fine forceps. Once units were isolated, the end of the hair shaft was placed inside a fire-polished 90 mm long glass capillary (1.2 mm outer diameter). The capillary was glued to a piezo trimorph slab measuring 35 mm x 6 mm x 0.6 mm. Using voltages between 10 and 200 V, the piezo was activated so that the end of the hair moved by up to 2 mm. The computer-controlled movements consisted of 5 s trapezoids, each with a 0.5 s onset ramp, a 4 s plateau, and a 0.5 s offset ramp. Each stimulus cycle lasted 30 s. Generally, two types of slowly adapting mechanoreceptor units(Gottschaldt et al., 1973) were encountered. St I units displayed irregular firing during the plateau phase, ceasing activity abruptly at the offset ramp – see trace at the top of Fig. 4. During the static phase (the last 1 s of the plateau) the inter-spike intervals were characteristically irregular, with a coefficient of variation (COV) > 0.1. In contrast, St II units showed regular firing throughout, COV < 0.1, and often continued to fire during the offset ramp, see trace at top of Fig. 5. These two unit types could further be identified pharmacologically by their characteristic response to 10 mM caffeine, 0.5 mM $BaCl_2$ and 3 mM tetraethylammonium (TEA) (Senok and Baumann, 1997, Senok et al., 2001, Senok and Cahusac, 2007).

Gated spikes, spike shapes and other events were recorded using a Power1401–3 scientific interface (Cambridge Electronic Design, Cambridge, UK). The number of spikes in different phases of response were counted. The dynamic phase consisted of the 0.5 s period during the ramp onset. The static phase consisted of the 1 s period during the last second of the plateau. The total number of spikes during the 5 s stimulus was also recorded, as was the number of spikes between ramp stimuli that represented spontaneous firing. A selected individual unit could be recorded continuously with stability for 6 h or more, although typically they were recorded for about 2.5 h. Different doses of the same drug were applied to the same unit following recovery of prior effects. Different drugs could also be applied to the same units following recovery from prior effects (one drug was studied in 19 units, 2 in 34 units, 3 in 8 units and 4 in 1 unit). At least 30 min washout was allowed between the termination of a drug application and a new application unless no effect of the drug was apparent (see Fig. 4). A new drug application was given when the activity (spontaneous and mechanically evoked) of the unit was stable without trend. Throughout the unit's study, mechanical stimulation was applied in continuous cycle (every

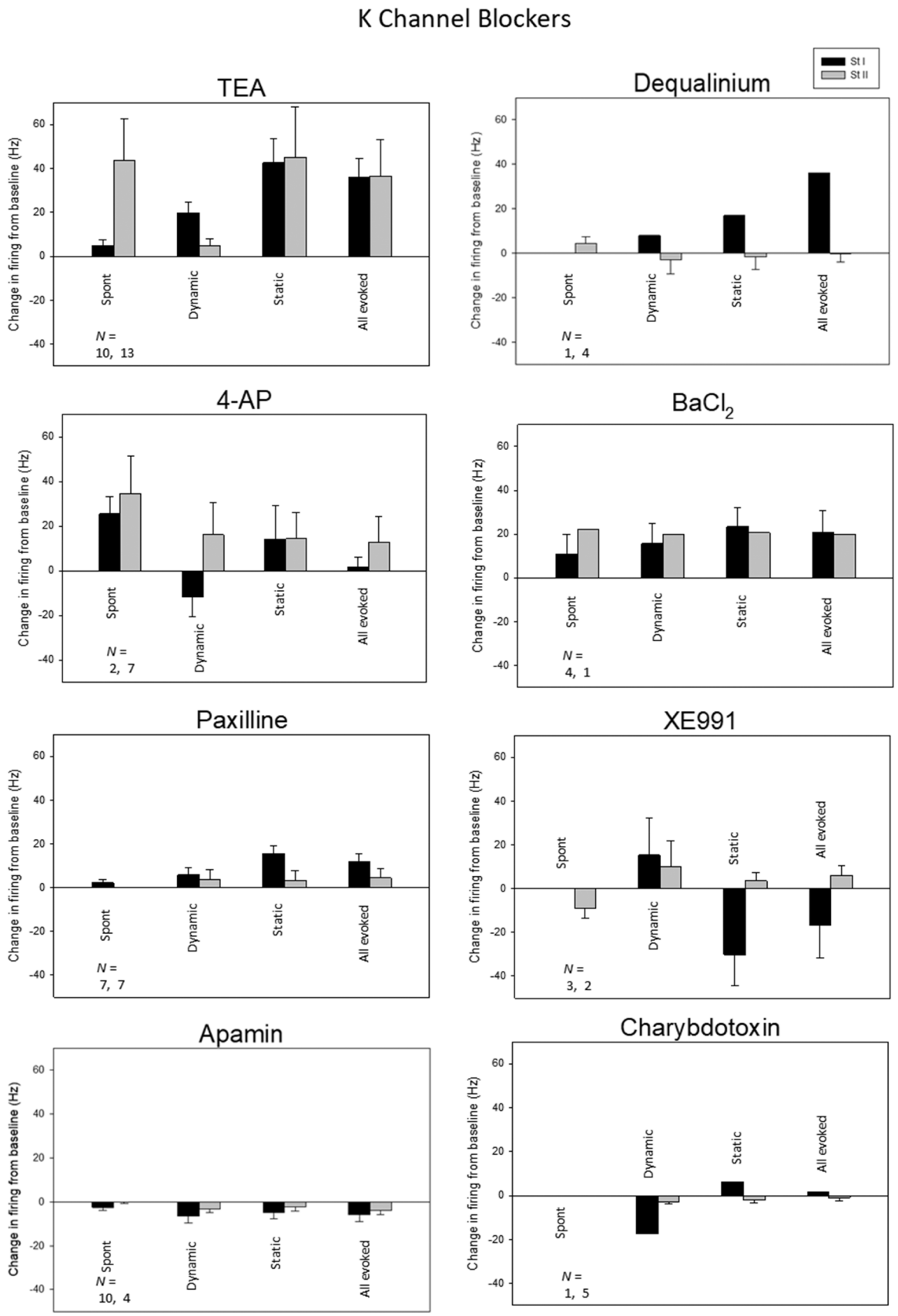

Fig. 1. Effects of K^+ channel blockers on St I and St II unit evoked and spontaneous firing. The different phases of activity are labelled in each bar graph. The type of unit is indicated by the bar fill (St I is black, St II is grey). Apamin is the only drug which consistently depressed firing. Sample sizes for St I and St II units are indicated below the bars for spontaneous activity, for example, for TEA there were 10 St I and 13 St II units. In both this and the next figure the error bars are standard errors.

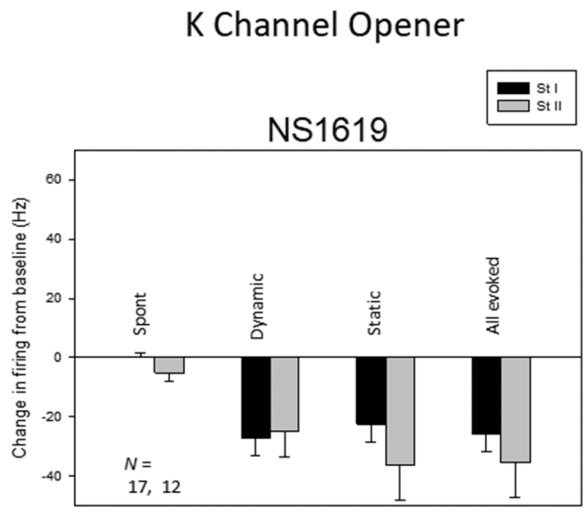

Fig. 2. Effects of K^+ channel opener NS1619 on St I and St II unit activity. The phases of activity are labelled above each bar cluster in each bar graph, and the type of unit is indicated by the bar fill (St I is black, St II is grey). As in Fig. 1 the sample size is indicated below the spontaneous bars, with 17 St I and 12 St II units.

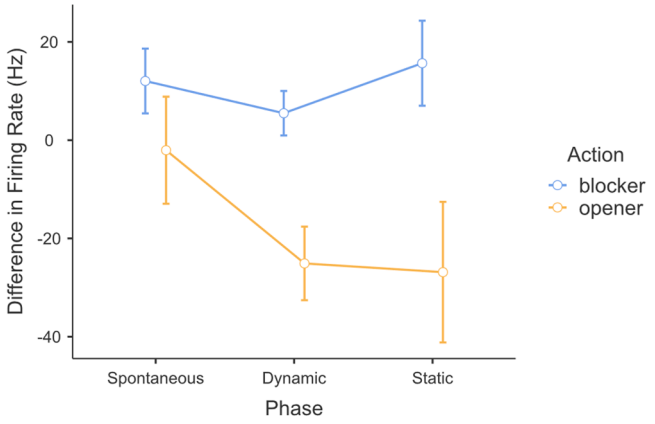

Fig. 3. Change in firing rate from before drug application for drugs classed as either K^+ channel blockers or opener (grey and black lines respectively). The changes are shown for each of the phases: spontaneous, dynamic and static. A clear interaction between the action of the drug and phase: blockers increased all activities while openers decreased evoked activities (dynamic and static) with less effect on spontaneous activity. Standard error bars are displayed. The sample sizes for St I were 39 blocker and 17 opener, and for St II there were 43 blocker and 13 opener experiments. Error bars are 95% confidence intervals.

30 s as explained above). This means that more than 720 ramp stimuli may be applied to the same unit (for more than 6 h of study). The direction and amplitude of stimulus ramp (up to 2 mm deflection) was chosen for each unit to provide the optimal response, preferably over 150 spikes per stimulus cycle.

Stock solutions of the following drugs were prepared: TEA (synthesized by Dr. E. Porter, Stirling, UK) 1 M in water, $BaCl_2$ (Sigma) 1 M in water, dequalinium (Tocris) 0.1 M in DMSO, 4-aminopyridine (4-AP) (Sigma) 1 M in water, paxilline (Tocris) 10 mM in DMSO, XE 991 dihydrochloride (Tocris) 50 mM in water, apamin (Tocris) 1 mM in water, charybdotoxin (Tocris) 50 μM in water, NS1619 (Sigma) 50 mM in DMSO. A summary of the drugs used, their site of action, typical effective concentration and concentration used in the present study is given in Table 1. Caffeine (Sigma) was made up freshly for each experiment by dissolving directly into SIF. Drug solutions were diluted in 20 ml of SIF at pH 7.4. Concentrations of DMSO were 0.6% or less, concentrations of ethanol were less than 0.7%. Drug solutions were introduced into the bath (approximate volume 4 ml) at a rate of 1 ml/minute. Generally, drug applications consisted of 20 ml of solution, although less was used if strong effects were observed early on in the application. The drug onset time was taken from the beginning of the application to when effects were first observed. The recovery time was taken from the termination of the drug application to when activity had returned to ± 15% of baseline.

Statistical analysis

Data was extracted from experiments using Spike2 software (version 8.21) into a Microsoft Excel datasheet. Data were transferred to jamovi (Version 1.6, retrieved from https://www.jamovi.org) for specific analyses. Mechanoreceptor unit firing for the different phases were converted to spikes/second (Hz). Averages from at least 3 trials were obtained before drug application, during the drug, and after removal of the drug (recovery). The average taken during the drug application was chosen where the maximal effect was seen, typically during the drug application, though occasionally the greatest effect was seen a few minutes after wash started. Most of the measures analyzed the difference data for 'during drug' with 'before drug' (during – before). Changes in response latency (first spike during the dynamic phase) were recorded, as was the time taken for onset and recovery of drug effects. The onset times varied from almost immediate (within 30 s) to more than 20 min, although generally, effects were seen within 10 min of introducing the drug in the bath. Recovery times could be within a few minutes, but generally, they were much longer.

The dose of drug was calculated by multiplying the natural logarithm of drug application time (in minutes) by the offset natural logarithm of the concentration. This resulted in positive values with an approximate normal distribution of drug dose.

Analyses involved ANOVA, ANCOVA and Welch's *t*-tests (where homogeneity of variance assumption is not required). Assumptions (e.g. sphericity, normality) were checked for all statistical procedures.

Results

A total of 62 units were isolated and recorded from; 29 were St I units and 30 St II units (3 could not be adequately defined). For St I units, the mean COV was 0.58, and was 0.07 for St II units.

A summary of the effects of all the drugs tested is given in Table 2.

Where adequate data were available, the data is plotted for the effects of each drug on different phases of neural activity, shown in Figs. 1 and 2. Fig. 1 gives the data for those drugs which appeared to increase firing and were known as K^+ channel blockers. Fig. 2 plots the data for the K^+ channel opener.

An overall analysis of the data used a repeated measures ANOVA, where phase of activity (spontaneous, dynamic, static) was the within-subjects factor, and drug (the 8 drugs for which sufficient data were available that appear in Fig. 1) and St type were between-subject factors. The dose of drug was a covariate. This analysis showed no obvious differences between drugs, $F(7, 65) = 1.68$, $p = .128$, partial $\eta^2 = 0.15$. None of the interactions between drugs, phase, St type approached statistical significance ($p > .147$, partial $\eta^2 < 0.10$.

A second repeated measures ANOVA was done, involving the type of K^+ channel action (blocker or opener), again using phase as the within-subjects factor, St type as factors, and dose was a covariate. Individual drugs were not identified in this analysis. Channel blockers were: $BaCl_2$, TEA, dequalinium, charybdotoxin, apamin, paxilline, 4-AP, XE 991; channel opener NS1619. The analysis showed that there was a clear difference between drugs $F(8, 93) = 7.97$, $p < .001$, partial $\eta^2 = 0.41$. This was due to the difference of the channel opener with the other 7 drugs, and revealed by the statistically significant interaction with phase $F(16, 186) = 2.13$, $p = .009$, $\eta^2 = 0.16$. This interaction is illustrated in Fig. 3. The general effect of the blockers was to increase the firing of

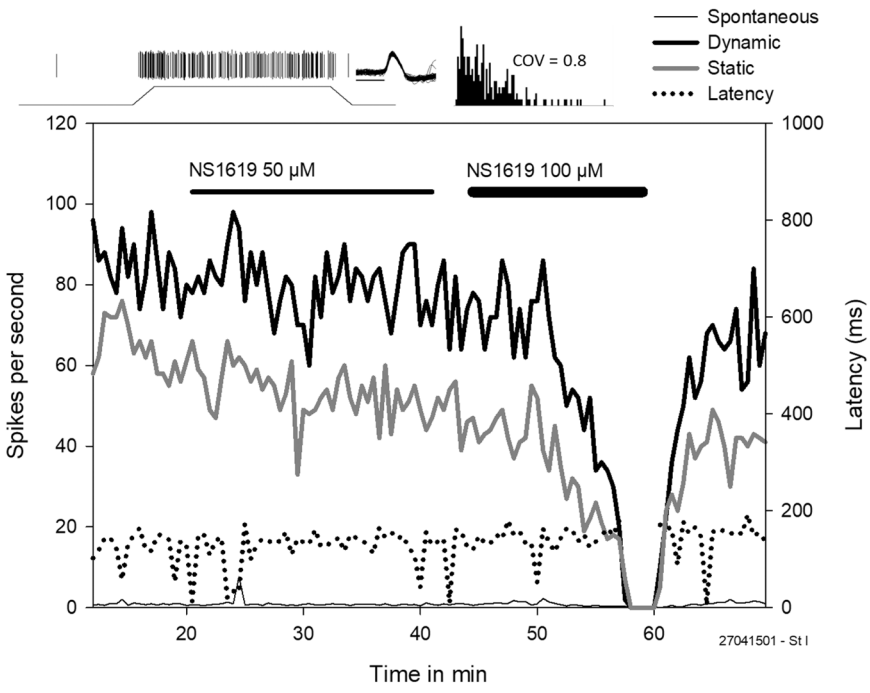

Fig. 4. Channel opener NS1619 tested on the activity of an St I unit. Drug applications are shown as horizontal bars above the traces. A low concentration, 50 µM, had little effect. After washing, a higher concentration of 100 µM had an obvious depressant effect on all phases of activity, after about 6 min. Recovery back to pre-drug levels of activity occurred after about 10 min from washing. The key at the top right of the figure indicates the style of lines used to depict the different phases of activity. Spontaneous is shown by a thin black line, dynamic as a thick black line, static as a thick grey line, and latency as a dotted line (scale given on right side). The action of the drug was to increase the latency of response; this is off the scale given. At the top left of the figure is shown a typical response of the unit to the 0.3 mm ramp (lasting 5 s). The unit response shows a characteristic sharp onset and offset of response, with the response continuing during the plateau phase of the ramp. Typical of the St I response was the irregularity of firing throughout the response. To the right of the trace is superimposed spikes from that typical response, the scale bar beneath is 1 msec, and the level of noise was 50 µV. To the right of that is an interval histogram plotting inter-spike intervals over 0.1 s, with bin size of 1 msec. Typical for an St I unit the intervals are spread widely, and the COV was 0.8.

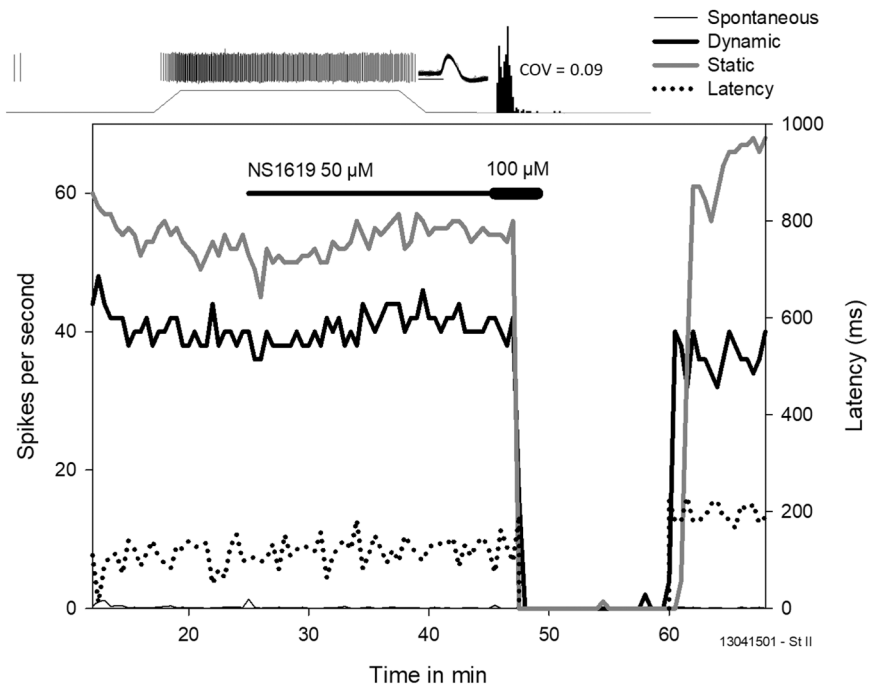

Fig. 5. The effect of NS1619 on an St II unit (COV = 0.09). A low concentration of 50 µM had little effect, while a higher concentration of 100 µM had strong depressant effects on all phases of activity. The depressant effect began withing 2.5 min of the application, and the application was terminated after 4 min. Recovery occurred after approximately 10 min. As in the previous figure, from the top left are shown a typical response to a 0.3 mm ramp. See previous figure for details. In contrast to the previous figure of an St I unit, this St II unit shows highly regular firing through its response to the ramp. This regularity is illustrated by the inter-spike interval plot shown further to the right, where most spikes were much closer to 0 than 0.1 s. As in the previous figure, response latencies exceeded the vertical axis scale, and are therefore not visible.

units within each of the phases, while the opener depressed evoked responses (dynamic and static) with less effect on spontaneous firing.

The channel opener drug increased the mean response latency time (1547 msec) compared with blocker drugs (−72 msec), $t(30) = 3.90$, $p = .0005$, Cohen's $d = 1.00$. NS1619 was also associated with longer recovery times (opener mean = 59 mins, blocker mean = 33 mins), $t(17) = 1.30$, $p = .209$, Cohen's $d = 0.45$.

A typical example of an experiment using a channel opener drug on an St I unit is given in Fig. 4. A low concentration (50 µM) of NS1619 had little effect on activity. When this increased to 100 µM all phases of activity were strongly reduced. Recovery occurred after about 10 min.

The channel opener NS1619 had a similar depressant effect on activity of an St II unit, see Fig. 5.

Individual examples of K^+ channel blockers on St I and St II units are shown in Figs. 6 and 7. Typically all activity is increased in St I units, although there was a general tendency to increase evoked responses more than spontaneous firing. Conversely, in St II units there was a general tendency to increase spontaneous firing equally or greater than evoked firing (see Fig. 1).

A few experiments tested cocktails of channel blocker and opener drugs. Two experiments examined the effects of TEA 1 mM with paxilline 50 nM. Only one of these produced some evidence that there was a

Table 1
Summary information about the drugs used in the present study.

K channel blockers	Site of action	Typical effective concentration	Concentration used here	References
Tetraethyl ammonium (TEA)	Voltage gated (6 T and 1 P), BK	10 μM - 10 mM	1 – 3 mM	(Riazanski et al., 2001)
4-aminopyridine (4-AP)	Voltage gated (6 T and 1 P)	10 μM - 10 mM	100 μM	(Riazanski et al., 2001)
Barium ions	Inwardly rectifying (Kir 3.x, Kir 1.1)	10 μM – 10 mM	100–500 μM	(Neyton and Miller, 1988)
Dequalinium chloride	Apamin-sensitive SK	1 – 10 μM	3 – 50 μM	(Liegeois et al., 2003)
Paxilline	BK, Voltage gated (6 T and 1 P)	.1 – 10 μM	0.01–10 μM	(Zhou and Lingle, 2014)
XE 991 dihydrochloride	Voltage gated – selective Kv 7	0.1 – 10 μM	10–100 μM	(Liu et al., 2018)
Charybdotoxin	BK, IK, Kv 1.x	10 – 100 nM	10 – 100 nM	(Laurent et al., 1993)
Apamin	SK	10 – 100 nM	0.1 – 3.5 μM	(Stocker et al., 1999)
K channel opener				
NS1619	Calcium activated K channel (BK_{Ca}) opener	10 – 100 μM	50 – 300 μM	(Ren et al., 2021)

Table 2
Summary statistics for all drugs tested in the study. The numbers of experiments are given in the 2nd to the last column.The shaded cells indicate those differences where $p < .01$ (but note that p values are strongly influenced by sample size). Mean values are given with standard error (SE) in brackets, if available.

				Changes in firing from pre-drug baseline						
Compound	*Concentration*	*Application time*	*St*	*Spontaneous*	*Dynamic*	*Static*	*All Evoked*	*Latency change (ms)*	*Duration (min)*	*N*
4-AP	0.1 - 1 mM	20.0	I	25 (7.7)	-12 (9)	14 (15.2)	2 (4.5)	-109 (39.3)	69 (8.5)	2
	0.01 - 1 mM	15.3	II	35 (16.7)	16 (14.6)	14 (11.6)	13 (11.5)	-48 (26)	33 (9.9)	7
TEA	1 - 10 mM	14.0	I	5 (2.6)	20 (4.8)	43 (11)	36 (8.4)	-96 (35.4)	19 (3.4)	10
	1 - 10 mM	10.3	II	43 (19.4)	5 (3.3)	45 (22.8)	37 (16.6)	-127 (26)	63 (14.8)	13
$BaCl_2$	500 μM	2.9	I	16 (12.8)	13 (13.8)	18 (9.3)	16 (12.5)	-666 (545)	14 (9.2)	4
	500 μM	2.5	II	22	20	21	20	-144	20	1
NS1619	50 - 300 μM	18.5	I	0 (1.4)	-27 (5.7)	-22 (6.2)	-26 (6.1)	1305 (512.7)	43 (7.6)	17
	50 - 200 μM	16.8	II	-5 (3)	-25 (8.7)	-36 (12.3)	-36 (11.7)	2018 (734.7)	90 (34.3)	12
apamin	0.1 - 3.5 μM	20.0	I	-3 (1.4)	-6 (3.3)	-5 (2.8)	-6 (3.1)	2 (251.6)	24 (5.6)	10
	1 - 3.5 μM	20.0	II	0 (0.6)	-3 (1.7)	-2 (1.8)	-4 (1.9)	19 (33.5)		4
charybdotoxin	0.01 μM	20.0	I	0	-17	6	2	35		1
	0.002 - 0.1 μM	20.0	II	0	-3 (1.3)	-2 (1.3)	-1 (1.4)	10 (8)		5
dequalinium	30 μM	20.0	I	0	8	17	36	6.0		1
	3 - 50 μM	20.0	II	5 (2.8)	-3 (6.4)	-2 (5.5)	0 (3.8)	-75 (83)		4
paxilline	0.01 - 10 μM	20.0	I	2 (1.6)	6 (3.1)	16 (3.5)	12 (3.8)	8 (17.9)	10 (1.9)	7
	0.01 - 10 μM	20.0	II	0 (0.1)	4 (4.6)	3 (4.5)	4 (4)	18 (12.4)		7
XE991	10 - 100 μM	20.0	I	0	15 (16.8)	-30 (14)	-17 (14.8)	4 (42.8)	23	3
	10 - 100 μM	20.0	II	-9 (4.5)	10 (12)	4 (3.7)	6 (4.8)	14 (0.8)	68	2

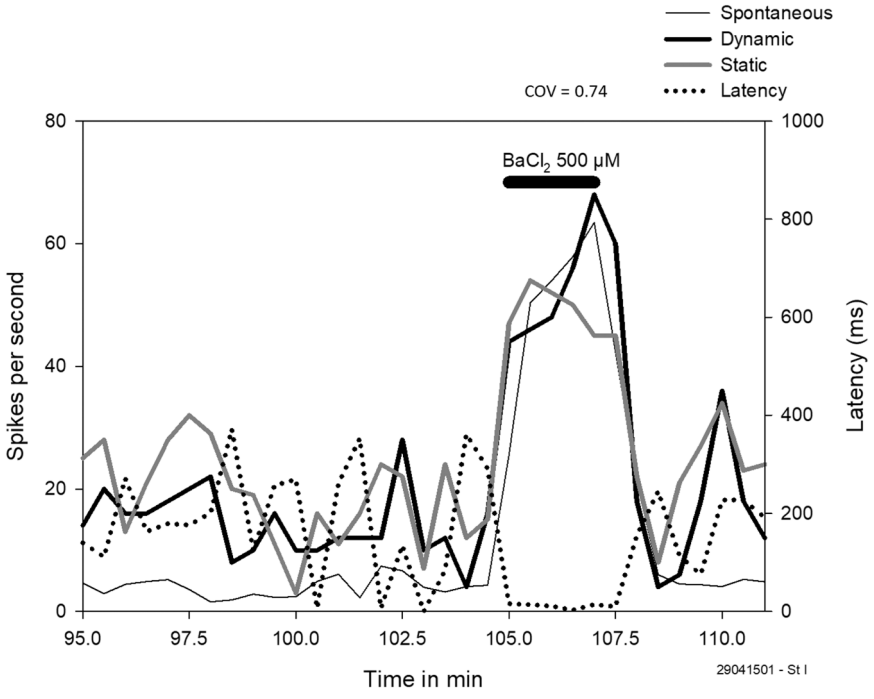

Fig. 6. The excitatory effect of K^+ channel blocker $BaCl_2$ 500 μM on an St I unit. The drug was applied for 2 min, the effect being seen within 30 s. Recovery to baseline occurred within 3 min of wash. See previous figures for details.

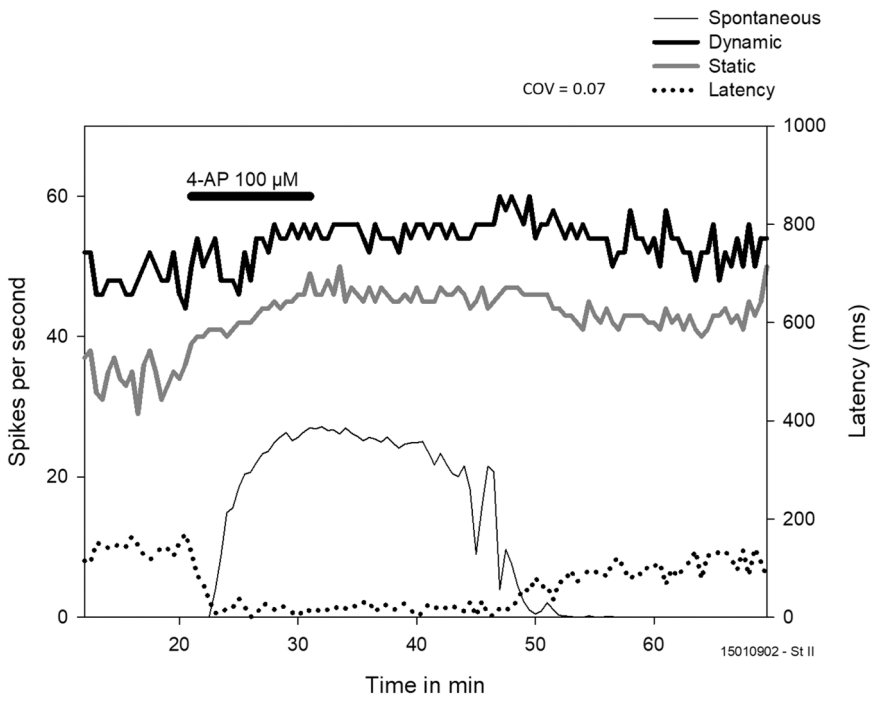

Fig. 7. The effect of K^+ channel blocker 4-AP 100 µM on the activity of an St II unit. As seen on other St II units with channel blockers, the effect on spontaneous firing was more pronounced than on other phases (evoked) activity. The drug was applied for 10 min, the excitatory effect becoming apparent after 2 min. Following wash, recovery occurred within 20 min, although evoked firing still appeared to be elevated for longer.

synergistic effect. A cocktail of paxilline 50 nM with NS1619 100 µM did not seem to prevent the depressant effect of NS1619. Finally, NS1619 100 µM did not appear to reduce the excitatory effect of TEA 1 mM. Further experiments could reveal interesting interactions.

Channel opener NS1619

An important aspect of this research is to compare St I and St II units. When just the data for NS1619 are analyzed, no difference between St I and St II was found, $F(1, 28) = 0.23$, $p = .632$, partial $\eta^2 = 0.01$. Although there was a clear difference across the 3 phases, $F(2, 56) = 16.44$, $p < .0001$, partial $\eta^2 = 0.37$, there was no difference between St type across the three phases of activity apparent: the interaction was $F(2, 56) = 1.33$, $p = .272$, partial $\eta^2 = 0.05$. The data are plotted in Fig. 8.

An analysis of effects of drug concentration and St type on all evoked activity did not produce a clear interaction between the factors, $F(2, 24) = 1.17$, $p = .328$, partial $\eta^2 = 0.09$. When a correlation is done between drug concentration and all evoked activity, this gives a negative relationship, $r = -0.398$, $p = .029$, $N = 32$: a clear dose-response relationship where the higher the concentration used the smaller evoked response compared with baseline, see Fig. 9.

Selected channel blockers: TEA, BaCl2, 4-AP and paxilline

The previous analyses included all the drugs, even those which did not appear to have clear excitatory or depressant effects. We selected 4

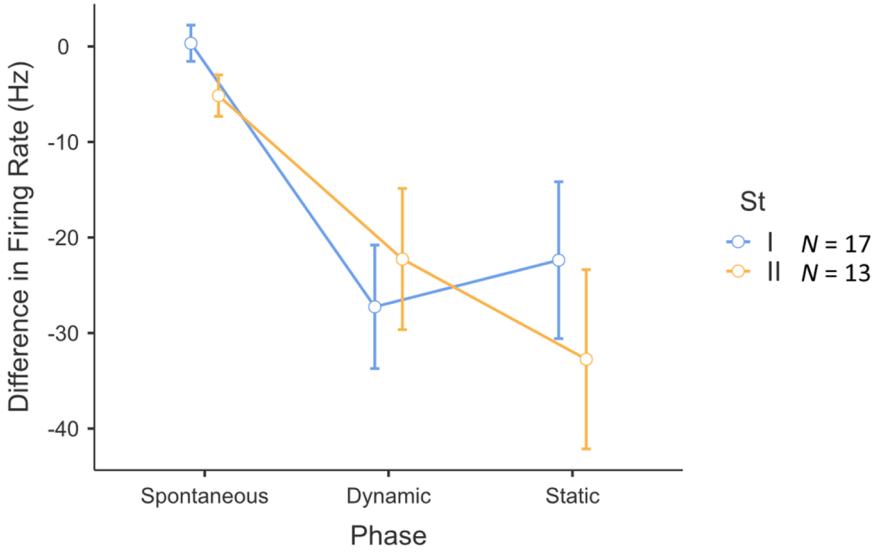

Fig. 8. Plot of difference from baseline in firing rates for different phases of activity produced by NS1619, 50 – 300 µM. Spontaneous firing is little affected, while both dynamic and static phases are strongly depressed. Error bars are 95% confidence intervals.

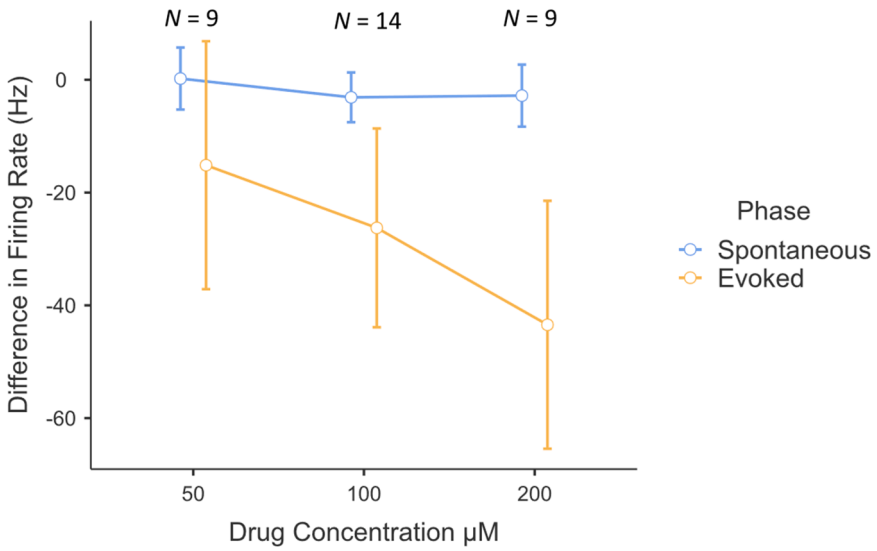

Fig. 9. Dose-response curve for the effects of NS1619 on spontaneous firing and evoked firing (differences from baseline). There is a clear dose-related depressant effect for evoked responses but no effect for spontaneous firing. The mean spontaneous firing rates at baseline varied from 2.9 to 5.1 spikes/sec, while those for evoked firing varied from 48.8 to 62.3 spikes/sec. The drug concentration is given as a logarithmic scale. Error bars are 95% confidence intervals.

channel blockers after looking at the data and examining Figs. 1 and 2. As we did previously (including the channel opener NS1619) we did a repeated measures ANOVA to examine the effects of the drugs on the different phases of activity and St type. No difference between St I and St II was found, $F(1, 50) = 0.48$, $p = .488$, partial $\eta^2 = 0.01$. There was a difference across the 3 phases, $F(2, 100) = 3.83$, $p = .020$, partial $\eta^2 = 0.07$, specifically between dynamic and static, $t(50) = 2.61$, $p = .031$ (Tukey test). No obvious difference between St type across the three phases of activity was apparent: the interaction was $F(2, 100) = 2.52$, $p = .086$, partial $\eta^2 = 0.05$. The data are plotted in Fig. 10. Despite the weak interaction, in individual experiments, it was noted that channel blockers did have specific effects according to St type. So, the evoked firing of St I units was relatively more enhanced than the spontaneous firing. For St II units, spontaneous firing was relatively more enhanced than evoked.

Dose-response data were plotted for TEA and paxilline, for which there was sufficient data, see Fig. 11 (A and B, respectively). Both drugs show clear reductions in their excitatory effects with higher doses.

A final figure, Fig. 12, shows the effects of the opener (NS1619) versus the blockers on different mechanoreceptor types (St I and St II) over different phases of response.

Discussion

A range of K^+ channel modulators was tested on rat sinus hair slowly adapting mechanoreceptors (St I and St II). We assessed the effects of the drugs on spontaneous and mechanically evoked firing. Spontaneous firing, the number of spikes between mechanical stimuli, is taken to indicate the resting excitability of the sensory ending, independent of its mechanosensory function. Our previous studies had shown that St II receptors were more prone to have spontaneous spiking activity (Baumann and Tsu, 1996, Senok et al., 1996)). The two phases of evoked firing, dynamic (stimulus ramping) and static (sustained stimulus application), represent the functional responsiveness of the receptor to

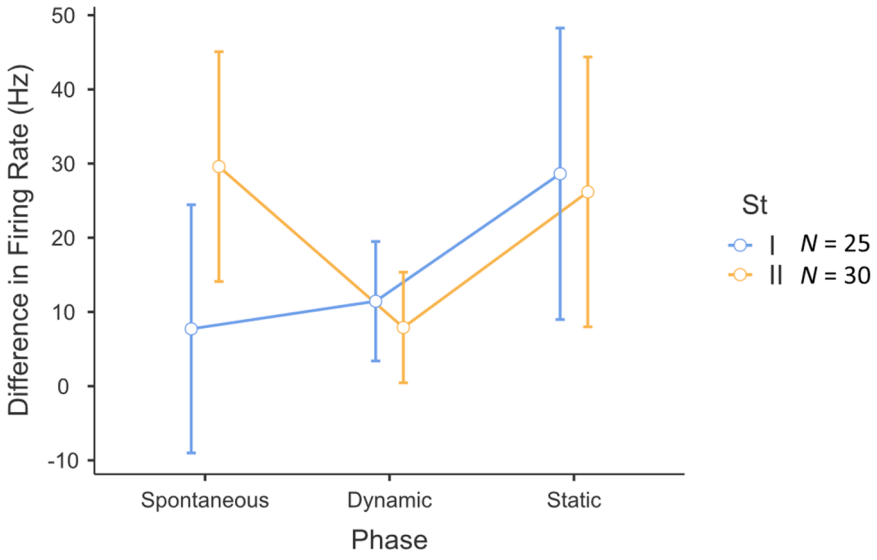

Fig. 10. Plot of difference from baseline in firing rates for different phases of activity produced by four K^+ channel blockers (TEA, $BaCl_2$, 4-AP, paxilline). The static phase was more enhanced than the dynamic phase, and there is an indication of an interaction between phase and St type by the difference between St I and St II effects for spontaneous firing. Error bars are 95% confidence intervals.

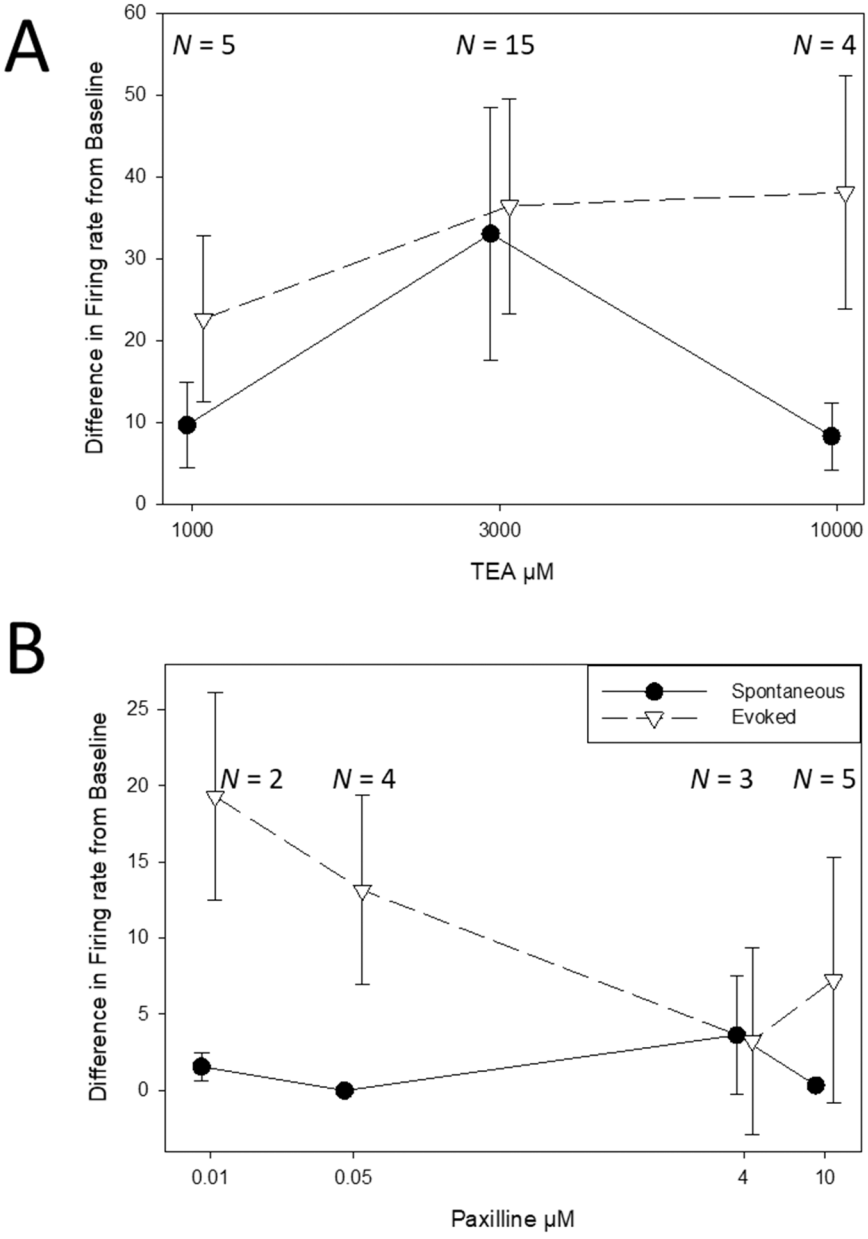

Fig. 11. Dose-response curve for the effects of TEA (A) and paxilline (B). As in the previous figure, spontaneous firing (filled circles) and evoked firing (white triangles). Standard error bars are displayed. The drug concentrations are given on a logarithmic scale. **A.** For TEA, there appears to be an inverted U-shaped relationship for the effects on spontaneous firing, with maximal excitatory effects at 1 mM. The effect on evoked responses seems to plateau at 1 mM. The mean spontaneous firing rates at baseline varied from 0.3 to 1.8 spikes/sec, while those for evoked firing varied from 38.6 to 70.6 spikes/sec. **B.** For paxilline, the lowest dose used of 10 nM appeared to have the most significant excitatory effect, specifically on the evoked firing. The mean spontaneous firing rates at baseline varied from 0.02 to 23.8 spikes/sec, while those for evoked firing varied from 52.9 to 70.9 spikes/sec.

adequate mechanical stimulation.

Our previous data showed that TEA selectively increases the static component of St I evoked responses, with less effect on the dynamic component or spontaneous firing (Senok and Cahusac, 2007). This contrasts with data obtained from the mouse where St I activity was unaffected by TEA up 10 mM (Sonekatsu et al., 2022), suggesting a possible species difference.

Since the normal role of BK channels may be to curtail transmitter release on mechanical stimulus termination, blockade of these channels would prolong transmitter release - in agreement with the increased static response we observed. The relatively low effective dose of TEA here is consistent with action at BK channels. Voltage-clamp recordings in isolated Merkel cells identified BK channels which, when blocked with TEA, increased intracellular calcium during hypoosmotic stimulation, although the duration of the effect was decreased (Piskorowski et al., 2008). The I_A type K^+ channels found in Merkel cells (KV4.2 and KV1.4) are also concerned with repolarisation and hyperpolarisation, and they are insensitive to TEA (>100 mM). In St II units, contrasting effects were found with TEA (1 – 3 mM): increased spontaneous firing and little or no effect on evoked responses (Senok and Cahusac, 2007), suggesting that the ongoing spontaneous spikes (characteristic of many St II/SA II units) arise from modulation of K^+ channel activity rather than mechanical perturbation.

The main findings of the study are that the K^+ channel blockers tested, as a group, increased mechanoreceptor responsiveness to mechanical stimulation (dynamic and static), as well as spontaneous firing (Fig. 3). Of the nine K blockers tested, five (TEA, dequalinium, 4-AP, $BaCl_2$, and paxilline) had consistent excitatory effects on neural activity, although differences were apparent between St I and St II receptors. For example, while dequalinium and paxilline increased responses of St I receptors while minimally influencing St II receptor responses, TEA and $BaCl_2$ excited both St I and St II to similar degrees (see Fig. 1). TEA and 4-AP had the most prominent effect on spontaneous firing, especially on St II receptors, where K blocker-induced spontaneous firing could last for over an hour after drug washout. Dequalinium and XE991, on the other hand, had minimal effect on spontaneous firing.

Previous work demonstrated that K^+ blockers could induce spontaneous firing in sensory neurons, independent of mechanical

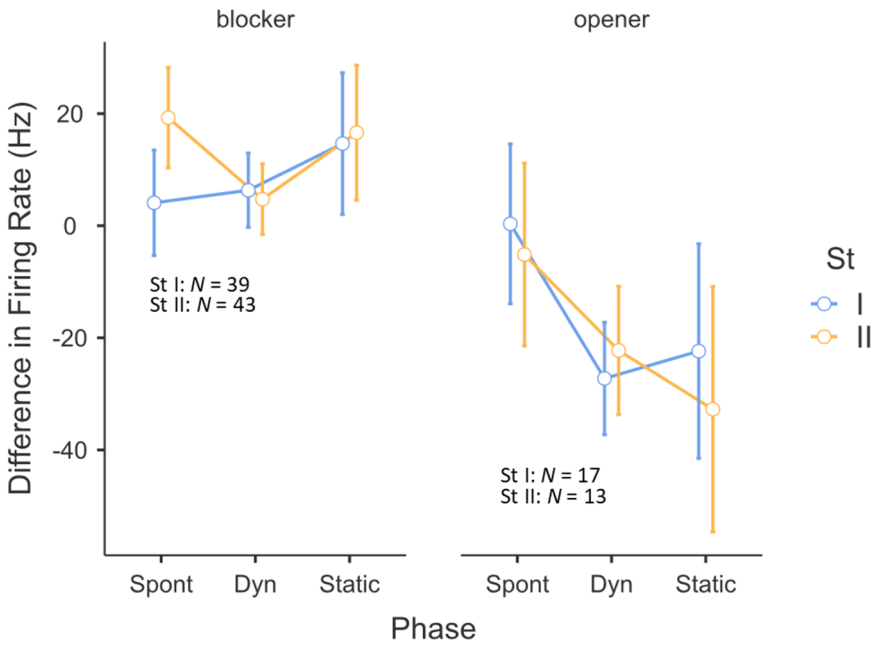

Fig. 12. The effects of the 8 channel blockers versus the channel opener NS1619 according to mechanoreceptor type (St I and St II, different colours, see key) and phase (spontaneous, dynamic and static, on horizontal axis). The vertical axis gives the mean difference in firing rate in Hz (during – baseline). The number of experiments for each type of unit are shown below each of the plots. Error bars are 95% confidence intervals.

responsiveness. TEA and 4-AP induced continuous discharges (spontaneous firing) in A-beta sensory endings in an in vitro rat skin-nerve preparation (Kirchhoff et al., 1992). Mesencephalic trigeminal sensory neurones developed sustained repetitive spiking when treated with 4-AP but not TEA (10 – 30 mM) (Negro and Chandler, 1997).

These effects of K^+ channel blockade on receptor excitability are consistent with the fact that K^+ channels regulate $E_{m;}$ hence a block makes them more responsive to mechanical stimulation. The increased responsiveness could be as a result of lowering the threshold for mechanical activation or making the receptors adapt more slowly. We observed both a change in latency (time to first spike) and an increase in static firing (see Table 2), reflecting threshold lowering and slowing of adaptation, respectively.

The different effects of the K^+ channel blockers most likely reflect the type of K^+ channel being blocked and their role in mechano-transduction. and likely differences in sensory transduction mechanism between St I and St II receptors. Several K^+ channel types have been reported in the presumed anatomical substrates of the sinus hair St I and St II receptors, Merkel cell neurite complexes and lanceolate endings, respectively (Yamashita et al., 1992). Among the K^+ channel activity or gene expressions are 4-AP, TEA and quinacrine sensitive currents in Merkel cells (Yamashita et al., 1992), K^+ channel subunits Kv4.1, Kv1.4, Kv1.8 in Merkel cells; large-conductance calcium-sensitive K channel (BK, (Haeberle et al. 2004, Piskorowski et al. 2008)). A wide array of K^+ channel types have been reported in primary afferents (see (Smith, 2020) for a recent review). The phenotypic expression of K^+ channels depends on their location, especially in polarized cells like primary afferents where the function can be different at the SC terminal, DRG cell body or cutaneous sensory ending. Utilising an in situ preparation such as the sinus hair preparation used in this study enables us to directly examine the potential roles of the different K^+ channels in mechanosensation.

Mechanotransduction in St I includes a neurotransmitter release step (Woo et al. 2015, Fechner and Goodman, 2018, Handler and Ginty, 2021). The role of BK channels in this component of evoked responses includes the coupling of calcium influx through mechanogated channels to K channel opening and rapid termination of transmitter release, a requirement for a receptor that responds so well to vibration (Kshatri et al. 2018). Blocking the BK channel in St I (TEA, BaCl, Paxilline, charybdotoxin), would be expected to increase evoked firing, especially the static phase, as observed in our experiments.

There was a poor correlation between the profile of effects against their reported potassium channel target. For example, paxilline and charybdotoxin (Matsumura et al., 2021) both target BK channels and yet the effects seen on St I and St II units differ markedly, see Fig. 1. Apamin also had little effect (slight depression of activity). It seems likely that this peptide (and paxilline and charybdotoxin) were unable to penetrate the tissue to bind to channels on the mechanoreceptors (Cahusac and Senok, 2020). Only 4 of the 9 channel blocker drugs tested, TEA, $BaCl_2$, 4-AP, paxilline, had clear enough effects. Typical effects included an increase in the spontaneous firing and evoked responses of the mechanoreceptor units. Despite their different targets (K_v and BK channels) their effects were reasonably similar. It is possible that at the doses used these drugs acted at the same channel to produce their similar action. Further work is required to distinguish more precisely the actions of these drugs. At similar concentrations to those used in the present study, a recent study in mice found that TEA and 4-AP had depressant effects on spontaneous and evoked firing (Sonekatsu et al., 2022). Apart from possible species differences, it is unclear why that study found depressant effects while we found clear excitatory effects.

Sufficient data were collected for the BK channel opener NS1619. This drug specifically decreased both phases of evoked firing, although its effects did not discriminate between the two St types, see Figs. 4 and 5. The action on Merkel cells is consistent with the prevention of release of transmitter (Hitchcock et al., 2004). However, the non-selective effect across the two St types might argue for a more general depressant effect on mechanoreceptor activation.

We used in excess of recommended doses to have their specific effects, yet many of the drugs used in this study failed to have clear effects on the different phases of firing of the mechanoreceptors studied. The lack of effect of some of the K^+ channel agents could be due to the inability of some compounds to access the mechanoreceptors protected by a collagenous capsule and mesenchymal sheath lining the thick basement membrane (Ebara et al., 2002). Facilitating access to mechanoreceptors remains a technical difficulty (Cahusac and Senok, 2020) that hampers their pharmacological study.

Statement of ethics

All procedures complied with the European Directive 86/609/EEC and royal decree no. 7/B/9512 dated 18/5/1422 H for the National Committee of Bioethics, Saudi Arabia. Ethical permission for the experiments were granted by Psychology Department Ethics committee of Stirling University and by the King Faisal Specialist Hospital and Alfaisal University IRB (# 2013-022).

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Author contributions

Dr Senok provided the ideas behind the research, while Dr Cahusac and Dr Senok carried out the research. Dr Cahusac analyzed the data and wrote the manuscript for publication. Dr Senok checked the final version of the manuscript before submission.

Data Availability

The data will be openly available as Supplementary information.

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Conflict of Interest Statement

There were no conflicts of interest for the two authors of this paper.

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