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Original Article

Effects of Lavender and Linalool on Neurotransmission and Contraction of Smooth Muscle

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ABSTRACT

Introduction: Lavender (*Lavandula angustifolia*) is commonly used in household products, perfumes, aromatherapy and complementary medicines. This study assesses the effects of lavender and its component linalool on neurotransmission and contraction of smooth muscle. **Methods:** The concentration-dependent effects of lavender (0.001% to 0.05%) and linalool (0.001% to 0.05%) on electrically evoked nerve terminal impulse (NTI) and excitatory junction current (EJC) amplitudes were assessed, while the effects of lavender (0.03%) and linalool (0.03%) on 5-hydroxytryptamine, acetylcholine, histamine, noradrenaline and oxytocin evoked responses were examined. Reversibility of lavender (0.03%) and linalool (0.03%) effects on electrically evoked NTI and EJC amplitudes, as well as on acetylcholine evoked contractile responses, were also analysed. **Results:** Lavender and linalool caused concentration-dependent decreases of electrically evoked NTI and EJC amplitudes, and attenuated the contractile responses towards 5-hydroxytryptamine, acetylcholine, histamine, noradrenaline and oxytocin. Repeated washing of tissues treated with lavender following pre-treatment with acetylcholine reversed the inhibitory effects of lavender, whereas linalool's effects were not readily reversible. **Conclusion:** Lavender and linalool may cause inhibition of smooth muscle presynaptic action potential propagation and postsynaptic G-protein coupled receptor evoked responses.

Key words: Excitatory junction current, G-protein coupled receptor, *Lavandula angustifolia*, Linalool, Nerve terminal impulse, Smooth muscle contraction, Synapses.

INTRODUCTION

Flowers of the common or English lavender plant (*Lavandula angustifolia*) are typically grown in gardens for their scent and purple-blue colours, and lavender is commonly used in household products, perfumes, aromatherapy and complementary medicines.[1,2] Lavender oil extracted from the flowers is a mixture of various chemicals, including short carbon-based chemicals and terpenes, with linalool comprising 39.6% to 41.2% of lavender.[3-5] Anecdotal accounts suggest that lavender brings about feelings of emotional and physical relaxation, while numerous studies have reported that lavender and linalool possess anti-inflammatory and antinociceptive properties.[6-13]

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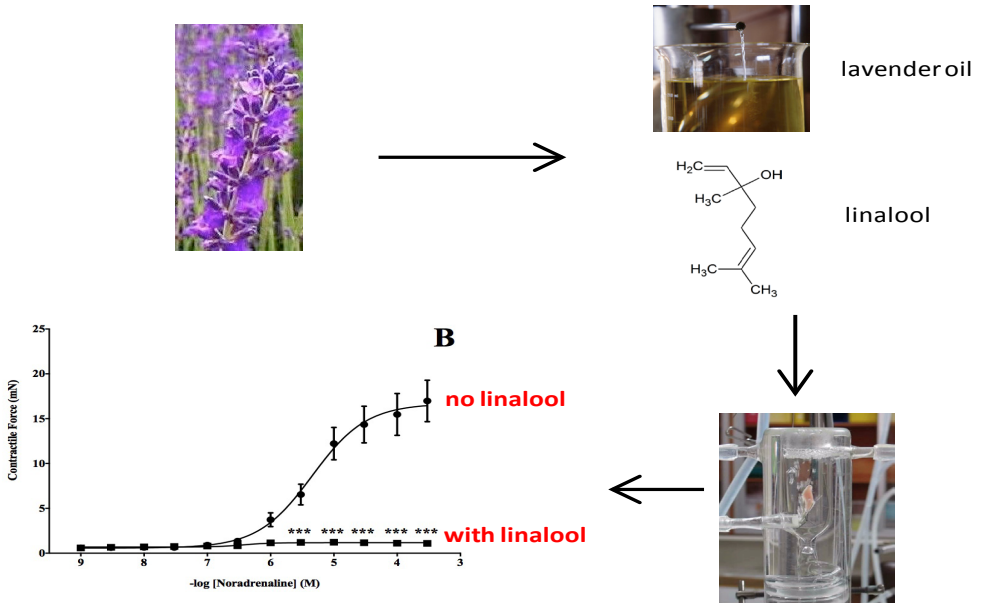
Lavender has been reported to exert presynaptic effects *ex vivo* with concentration-dependent decreases rat hemidiaphragm contractile forces caused by phrenic nerve stimulation.[14,15] In addition, the postsynaptic effects *ex vivo* of are reported to cause (1) relaxation of electrically stimulated and acetylcholine or histamine pre-contracted guinea pig ilea, (2) decreased amplitudes of evoked neurotransmission of mouse hemidiaphragms, and (3) concentration-dependent reductions of directly electrically stimulated rat hemidiaphragm twitch responses and electrically evoked and rhythmic contractions of guinea pig ilea.[15-17] Proposed mechanisms for lavender's effects include intracellular pathway changes, reduction of free



Graphical Abstract

intracellular calcium ion concentrations, effects upon the cell membrane, and sodium and calcium channels.[14,15,18,19]

Linalool has also been shown to have presynaptic effects *ex vivo* upon rat hemidiaphragms stimulated via the phrenic nerve.[14,15] It also reduces voltage-gated currents of the newt olfactory receptor and retinal horizontal and ganglion cells, and voltage-gated channel openings in rat cerebellar Purkinje cells.[20] Linalool has been shown to act in a concentration-dependent manner to decrease compound action potential amplitudes of frog and rat sciatic nerves, intact rat dorsal root ganglion neurons and sodium current amplitudes of dissociated rat dorsal root ganglion neurons.[21,22] Proposed mechanisms for linalool include effects upon the cell membrane and the opening of presynaptic voltage-gated calcium, potassium and sodium channels.[17,19-23]

Due to ongoing interest in the use of lavender and linalool for smooth muscle relaxation, the present study compares and contrasts their concentration-dependent effects and their reversibility at presynaptic and postsynaptic sites of action. Firstly, the concentration-dependent effects of lavender and linalool on smooth muscle electrically evoked nerve terminal impulse (NTI) and excitatory junction current (EJC) amplitudes were investigated. Secondly, lavender and linalool effects on 5-hydroxytryptamine (5-HT), acetylcholine, histamine, noradrenaline and oxytocin evoked contractions of smooth muscle were assessed, along with their reversibility. Collectively, this study attempted to obtain information on the effects of lavender and linalool on neurotransmission and contraction of smooth muscle.

MATERIALS AND METHODS

Chemicals

Lavender oil (*Lavandula angustifolia* Pure Lavender Oil, 100% purity) was produced by Dematin Pty Ltd (Nabowla, Australia). Linalool ((±)-Linalool, ≥ 95% purity), 5-HT (Serotonin creatinine sulfate complex), acetylcholine (Acetylcholine chloride, ≥ 99% purity), histamine (Histamine bisphosphate monohydrate) and noradrenaline (L-(−)-Norepinephrine (+)-bitartrate salt monohydrate, ≥ 98% purity) were produced by Sigma-Aldrich Corp. (St Louis, Missouri). Oxytocin (Ilium syntocin, 10 IU/ml) was produced by Troy Laboratories Pty Ltd (Sydney, Australia). Concentrated lavender and linalool were each diluted in buffer to create lavender or linalool physiological buffer solutions at concentrations ranging from 0.001% to 0.05%. These solutions were mixed well prior to their application to tissues.

Concentrations of lavender and linalool are expressed as a percentage by volume, and it is important to note that lavender itself is a variable mixture of chemicals, including linalool.[3-5,24-26] In experiments that examined a single concentration of lavender or linalool, a concentration of

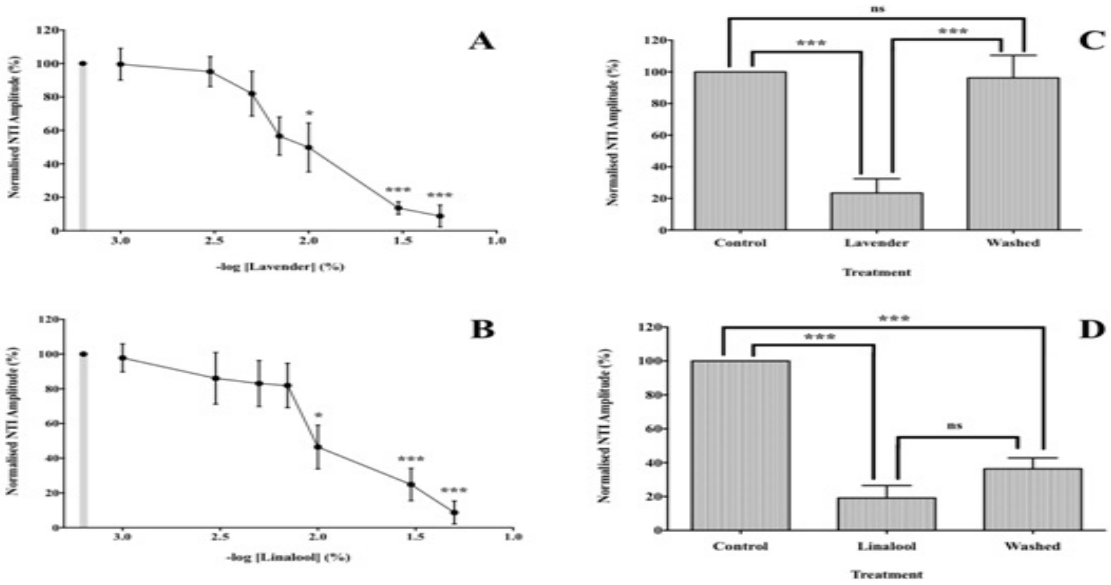


Figure 1: The effects of 0.001-0.05% lavender (A) and linalool (B) and reversibility of these effects (C and D for 0.03% lavender and linalool, respectively) on electrically-evoked nerve terminal impulse (NTI) amplitudes of mouse ductus deferentes. A and B show electrically-evoked NTI amplitudes normalised to control (100%) values (represented as bars). C and D show electrically evoked NTI amplitudes without (Control) and with lavender (C) and linalool (D), and after thorough washing of the tissues with buffer solution (Washed)

Results are expressed as mean amplitudes ± SEM for six individual experiments. *=p<0.05, ***= p<0.001, ns= not significant

0.03% was examined as this concentration of lavender has been reported to bring about a sensation of relaxation when administered odorously.[27]

Animals

Inbred male C57BL/6J mice (*Mus musculus*, 6 weeks postnatal) were used for electrophysiological experiments. Out bred Wistar rats (*Rattus norvegicus*, 11 weeks postnatal) were used for organ bath experiments, with males being used for experiments that examined the effects of 5-HT and acetylcholine on ilea and noradrenaline on ductus deferentes and naïve females being used for experiments that examined the effects of oxytocin on uterine horns. Out bred male Tricolour guinea pigs (*Cavia porcellus,* 400 g to 600 g) were used for organ bath experiments that examined the effects of histamine on ilea, as guinea pig ilea express greater numbers of histamine receptors than rat ilea.[28] All rodents were housed within rooms maintained on a 12 hour day/night cycle at room temperature, with food and water available *ad libitum*. Animal ethical clearance was granted by the Animal Ethics Committee at the University of Queensland (Australia).

All rodents were sacrificed by cervical fracture, with mice and rats being first anesthetised with CO_2, after which the tissue of interest was removed. Ductus deferentes were bisected and only the prostatic section was used for experimentation. Uterine horns were also bisected, and ilea were cut into sections approximately 2 cm in length.

Electrophysiological and Contractile Experimentation

The electrophysiology experiments were conducted as described previously.[29] Tissue contraction experiments involved mounting tissues into organ baths where ductus deferentes and ilea were bathed in contractile Tyrode's solution (32°C) and uterine horns bathed in Kreb's solution (37°C). 5-HT concentrations ranging from 1×10^{-9} M to 3×10^{-5} M, and acetylcholine, histamine and noradrenaline concentrations ranging from 1×10^{-9} M to 3×10^{-4} M were tested on tissues both in the absence and the presence of lavender or linalool. Oxytocin concentrations ranging from 1×10^{-5} IU/ml to 3×10^{-2} IU/ml were examined from lowest to highest using cumulative concentrations at 3-minute intervals both in the absence and the presence of lavender or linalool. Twelve individual experiments were performed in the absence of lavender or linalool and nine individual experiments were performed in the presence of lavender or linalool (n=12 for control; n=6 for each chemical). Data were plotted using Graph Pad Prism® (Version 5.04, Graph Pad Software Inc., San Diego).

Statistical Analyses

The statistically significant effects of lavender and linalool on electrically evoked NTI and EJC amplitudes, and the

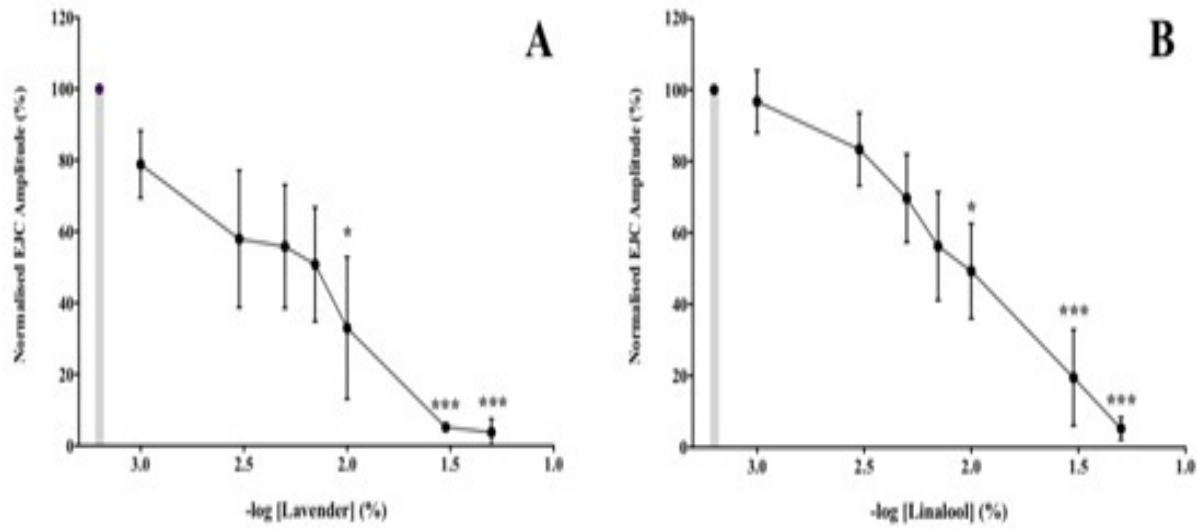


Figure 2: The effects of 0.001-0.05% lavender (A) and linalool (B) on electrically evoked excitatory junction current (EJC) amplitudes of mouse ductus deferentes. Amplitudes were normalised relative to the control (100%) values (represented as bars). The control is shown above the filled grey bar

Results are expressed as mean amplitudes ± SEM for six individual experiments. * = p<0.05, *** = p<0.001

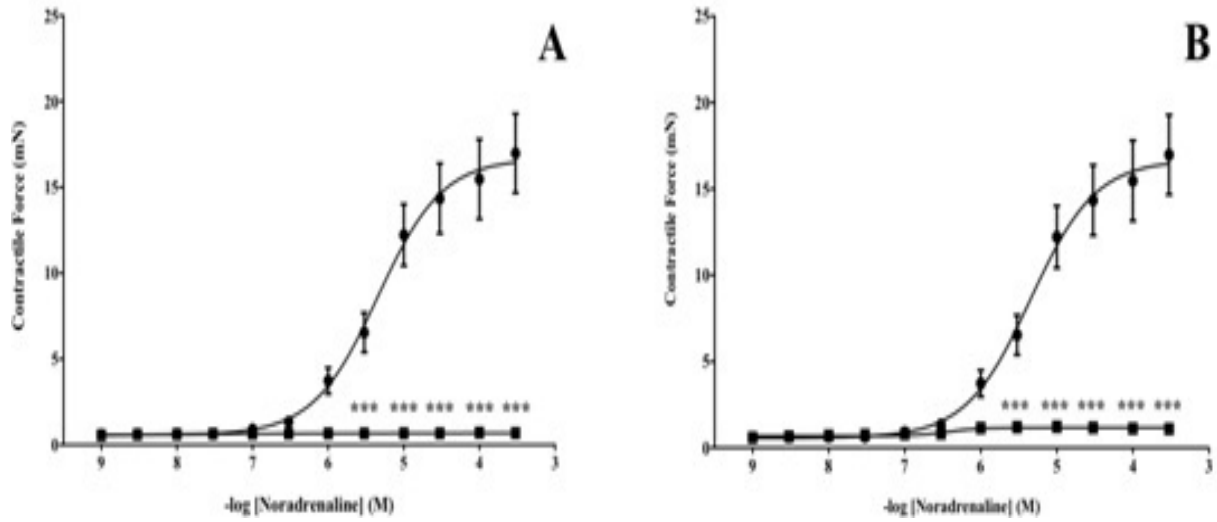


Figure 3: Effects of 0.03% lavender (A) and linalool (B) on noradrenaline-evoked contractions of rat ductus deferentes. Circles indicate contractile forces measured in the absence of compounds (controls), while squares indicate contractile forces in the presence of lavender or linalool

Results are expressed as mean contractile forces ± SEM for twelve (controls) or six (lavender and linalool) individual experiments. *** = p<0.001

reversibility of electrically evoked NTI amplitudes and acetylcholine and noradrenaline evoked contractile forces, were determined using an unpaired two-tailed one-way analysis of variance with a Tukey's multiple comparison post-test. The statistically significant effects of lavender and linalool on 5-HT, acetylcholine, histamine and noradrenaline evoked contractile forces and oxytocin evoked increases of minimum tensions were determined using an unpaired two-tailed two-way analysis of variance with a Bonferroni post-test. Statistical analyses were conducted using Graph Pad Prism® (Version 5.04).

RESULTS

NTI Amplitudes

The effects of lavender and linalool were examined at concentrations ranging from 0.001% to 0.05% on the electrically evoked NTI amplitudes of mouse ductus deferentes. Both lavender and linalool caused statistically significant concentration-dependent decreases of electrically evoked NTI amplitudes relative to the respective control at concentrations ranging from 0.01% to 0.05%

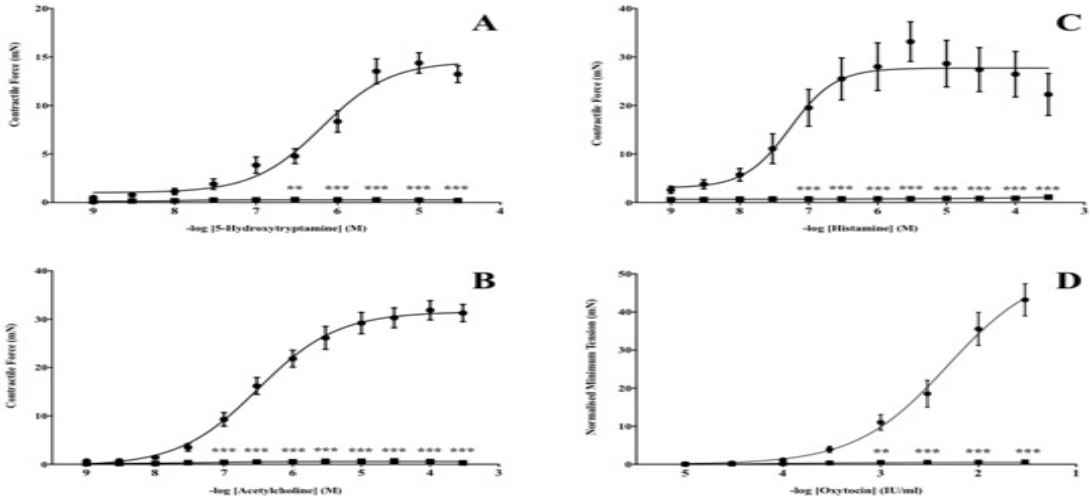


Figure 4: Effects of 0.03% linalool on contractions of rat ilea evoked by 5-HT (A) and acetylcholine (B), guinea pig ilea by histamine (C) and rat uterine horns by oxytocin (D). Circles indicate responses measured in the absence of linalool (controls) while squares represent responses in the presence of linalool

Results are expressed as mean responses ± SEM for twelve (controls) or six (linalool) individual experiments. "** = p<0.001"

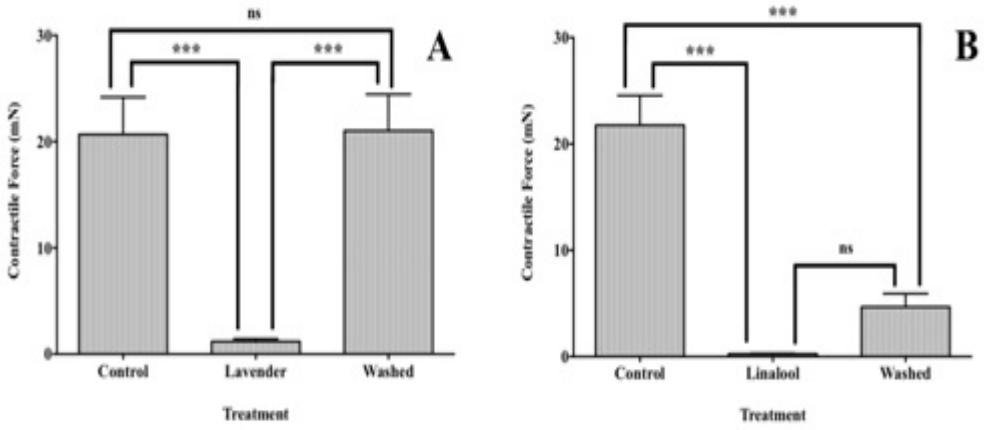


Figure 5: Reversibility of 0.03% lavender (A) and linalool (B) on acetylcholine-evoked contractions of rat ilea. contractile forces were obtained without (Control) and with lavender (A) and linalool (B), and then after thorough washing of the tissues with buffer solution (Washed)

Results are expressed as mean acetylcholine evoked contractions ± SEM for six individual experiments. *** = p<0.001, ns=not significant

($p<0.05$; n=6 for each chemical; Figures 1A and 1B). As such decreases might be attributed to tissue damage, the reversibility of lavender and linalool was also tested. After lavender was washed from the ductus deferentes, there were no statistically significant differences between the electrically evoked NTI amplitudes relative to the respective control ($p>0.05$; n=6; Figure 1C). Conversely, after linalool was washed from the ductus deferentes, statistically significant differences were observed between electrically evoked NTI amplitudes relative to the respective control ($p< 0.05$; n=6; Figure 1D). Thus, lavender effects were reversible, whereas linalool's effects were not.

EJC Amplitudes

Similarly, both lavender and linalool were examined at concentrations ranging from 0.001% to 0.05% on the electrically evoked EJC amplitudes of mouse ductus deferentes. As with their effects on electrically evoked NTI amplitudes, both lavender and linalool caused statistically significant concentration-dependent decreases of electrically evoked EJC amplitudes relative to the respective control at concentrations ranging from 0.01% to 0.05% ($p<0.05$; Figure 2).

Noradrenaline Evoked Contractile Forces

Increasing concentrations of noradrenaline generated a sigmoidal contraction curve with an EC_{50} of 4.53×10^{-6} M (n=12; Figure 3). Lavender and linalool caused statistically significantly decreases of noradrenaline evoked contractile forces at concentrations ranging from 3×10^{-6} M to 3×10^{-4} M, producing comparatively higher EC_{50} val-

ues for lavender (8.73×10^{-7} M) and linalool (3.70×10^{-7} M) ($p<0.05$; n=6 for each chemical; Figure 3).

Contractile Forces and Minimum Tensions Evoked by Other Neurotransmitters

As was done for noradrenaline, the effects of lavender and linalool at a concentration of 0.03% were examined on 5-HT, acetylcholine and histamine evoked contractile forces and oxytocin evoked increases of minimum tensions. 5-HT (1×10^{-9} M to 3×10^{-5} M) and acetylcholine (1×10^{-9} M to 3×10^{-4} M) were tested on rat ilea, whereas histamine (1×10^{-9} M to 3×10^{-4} M) was tested on guinea pig ilea. Oxytocin (1×10^{-5} IU/ml to 3×10^{-2} IU/ml) was tested on rat uterine horns. The overall increase of contractile forces and minimum tensions with increasing concentrations of the these agonist compounds followed a sigmoidal curve, with the EC_{50} for 5-HT being 6.41×10^{-7} M, acetylcholine being 3.14×10^{-7} M, histamine being 5.37×10^{-8} M and oxytocin being 4.84×10^{-3} IU/ml (n=12 for each agonist; Figure 4).

In the presence of 0.03% lavender or linalool, significant decreases of 5-HT evoked contractile forces occurred at concentrations ranging from 1×10^{-6} M to 3×10^{-5} M ($p<0.05$; n=9 for each chemical; Figure 4A; data for lavender not shown). They also significantly reduced acetylcholine and histamine evoked contractile forces at concentrations ranging from 1×10^{-7} M to 3×10^{-4} M ($p<0.05$; n=9 for each chemical; Figures 4B and 4C; data for lavender not shown). The increases in minimum tensions caused by oxytocin were also significantly reduced in the presence of 0.03% lavender or linalool at oxytocin concentrations ranging from 3×10^{-3} IU/ml to 3×10^{-2} IU/ml ($p<0.05$; n=6 for each chemical; Figure 4D; data for lavender not shown).

Reversibility of Inhibitory Effects of Lavender and Linalool

As shown in Figure 5A, rat ilea contractions evoked by acetylcholine were reduced by lavender, but returned to control values following repeated washes with Tyrode's buffer solution ($p<0.05$; n=6). However, this is not the case with linalool, where the acetylcholine evoked contractile forces inhibited by linalool failed to return to control values despite repeated washing with Tyrode's solution ($p>0.05$; n=6; Figure 5B). This suggests that the inhibitory effects of linalool on smooth muscle tissue are irreversible.

DISCUSSION

We observed statistically significant concentration-dependent decreases of electrically evoked NTI amplitudes of mouse ductus deferentes by lavender and linalool. This may suggest that these chemicals cause concentration-dependent inhibition of the propagation of action potentials along the axons innervating smooth muscle cells, as indicated in earlier studies.[30-32] The effects of linalool are supported by earlier findings showing that linalool decreased the amplitudes of evoked neurotransmission of mouse hemidiaphragms.[17] Linalool has been found to have many other neurophysiological effects. It non-selectively depresses voltage-gated currents of newt olfactory receptor cells, inhibits voltage-gated currents of newt retinal horizontal and ganglion cells, and inhibits voltage-gated channel opening in rat cerebellar Purkinje cells.[20] Linalool causes concentration-dependent depressant effects on compound action potential amplitudes of rat sciatic nerves and intact rat dorsal root ganglion neurons, as well as sodium current amplitudes of dissociated rat dorsal root ganglion neurons.[21] It can also suppress compound action potential amplitudes of frog sciatic nerves.[22] Our findings with lavender also support previous studies that have demonstrated attenuation of electrically evoked NTI amplitudes,[14-15] including the concentration-dependent relaxation of rat hemidiaphragms when electrically stimulated via the phrenic nerve.[14] It is likely that lavender and linalool attenuate electrically evoked NTI amplitudes by non-specific inhibition of axonal voltage-gated sodium channels. Together, these findings suggest that both lavender and linalool have a local anaesthetic-like effect.

Lavender and linalool caused statistically significant concentration-dependent decreases of electrically evoked EJC amplitudes of mouse ductus deferentes. An EJC is a depolarisation within a smooth muscle cell generated by exocytosed adenosine 5'-triphosphate binding to, and subsequently opening, $P2X_1$ receptor ligand-gated cation channels localised within the smooth muscle cell membrane, facilitating an influx of cations into this smooth muscle cell.[33-36] Thus, it is possible that lavender and linalool cause a concentration-dependent decrease in the flow of cations through $P2X_1$ receptor ligand-gated cation channels and subsequently cause concentration-dependent attenuation of the generation of local depolarisations within smooth muscle cells.It is, however, unlikely that lavender or linalool specifically inhibit $P2X_1$ receptor ligand-gated cation channels, as this typically requires a highly specific molecular structure for channel binding.[3-5,37]

Noradrenaline evoked concentration-dependent increases of contractile forces, which were diminished in the presence of lavender and linalool. This was also observed for 5-HT, acetylcholine, histamine and oxytocin evoked responses in the presence of a concentration of 0.03% lavender and linalool. While this study did not specifically

examine the mechanisms by which lavender and linalool decreased smooth muscle G-protein coupled receptor (GPCR) mediated contractile forces and minimum tensions, it is well established that all agonists examined cause tissue contractions via activation of the G_q subfamily signalling pathway. Noradrenaline evokes contractions of mouse and rat ductus deferentes by binding primarily to α_{1A} GPCRs, which mediate their effects primarily via the G_q subfamily.[38-40] 5-HT evokes contractions of rat ilea by binding primarily to 5-HT_{2B} GPCRs, which mediate their effects via the G_q subfamily.[41-44] Acetylcholine evokes contractions of rat ilea primarily via the M_3 GPCR but also to a lesser extent via the M_2 GPCR, which enhances the effect of the M_3 GPCR, with the M_2 GPCR expressed at four-fold higher levels than the M_3 GPCR.[45] M_2 GPCRs mediate their effects primarily via the G_i subfamily but also via the G_q subfamily and G_s, and M_3 GPCRs mediate their effects via the G_q subfamily.[46-50] Histamine contracts guinea pig ilea by binding primarily to H_1 GPCRs, which mediate their effects via the G_q subfamily,[51-53] while oxytocin increases tension within rat uterine horns by binding to OT GPCRs, which mediate their effects primarily via the G_q subfamily but also via the G_i subfamily.[54,55]

The activation of G_q subfamily GPCRs leads to an increase of the cytosolic concentration of calcium ions and subsequently causes the translocation of cytosolic phospholipids $A_2\alpha$ to the smooth muscle cell membrane.[56,57] Phosphorylation of cytosolic phospholipids A_2 α by specific kinases subsequently causes the hydrolysis of phospholipids of the smooth muscle cell membrane, thereby generating arachidonic acid.[58] Arachidonic acid is converted into prostaglandin G_2, which is subsequently converted into prostaglandin H_2 by prostaglandin-endo peroxide synthase-1 under physiological conditions.[59,60] Prostaglandin H_2 is subsequently converted into prostaglandin $F_{2\alpha}$ by prostaglandin-F synthase.[59,61] Prostaglandin $F_{2\alpha}$ evokes increases of the tension of non-pregnant rat uterine horns by binding primarily to FP GPCRs localised within the myometrium, which mediate their effects primarily via the G_q subfamily but also via G_s.[62-64] While the present study did not specifically examine the mechanisms by which lavender and linalool decrease smooth muscle GPCR evoked contractile forces and minimum tensions, we should note that all agonists examined evoked the respective aforementioned response via activation of the G_q subfamily signalling pathway. Therefore, it is possible that lavender and linalool inhibit the G_q subfamily signalling pathway via at least one mechanism common to all smooth muscle types examined. We also cannot dismiss the possibility that there is a site common to all smooth muscle types examined that, when affected by lavender or linalool, can decrease smooth muscle contraction.

Lavender is a mixture of various chemicals, including linalool (approximately 40% content),[3-5] however both lavender and pure linalool generally exerted similar effects on the smooth muscle examined. One notable exception is the reversibility of lavender's attenuation of electrically-evoked NTI and EJC amplitudes and tissue contractions caused by acetylcholine. This was found to be irreversible when linalool was applied to the tissues. The reasons behind this phenomenon remain unclear and require further study. It suggests that lavender extract contains compound(s) that abolish the irreversible inhibition of tissue contraction caused by linalool. This finding, alongside linalool's powerful inhibitory effects on tissues co-administered with agonists (5-HT, acetylcholine, histamine, noradrenaline and oxytocin) provide evidence that linalool is the primary, biologically active component of lavender.

CONCLUSION

The mechanisms of action of lavender and linalool appear to be multi-factorial and lead to the inhibition of presynaptic action potential propagation and postsynaptic GPCR-evoked responses in different smooth muscle tissue types. Our findings support earlier studies documenting the anti-inflammatory and antinociceptive properties of lavender,[6-13] and that the mechanisms outlined in the present study may underlie the smooth muscle relaxation and analgesic properties of products containing lavender or linalool.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENT

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ABBREVIATIONS

NTI : nerve terminal impulse
EJC : excitatory junction current
5-HT : 5-hydroxtryptamine
GPCR : G-protein coupled receptor.

Highlights of Paper

- Lavender and linalool decreased electrically evoked nerve terminal impulse amplitudes and electrically evoked excitatory junction current amplitudes.
- Lavender and linalool decreased 5-hydroxytryptamine, acetylcholine, histamine, noradrenaline and oxytocin evoked contractile responses.
- Lavender's effects on smooth muscle contraction were reversible whereas linalool's effects were not readily reversible.
- Lavender and linalool cause smooth muscle relaxation via several mechanisms and thus have potential therapeutic applications.

Author Profile

- Curtis Poyton is the director of Medical Compliance, an Australian corporation that implements and keeps up-to-date policies and procedures tailored to Australian medical practices and their staff, through the ongoing provision of information, advice, assistance, training and documentation. He completed his PhD in the field of Pharmacology at The University of Queensland, Australia where he examined the effects of plant-derived chemicals on smooth muscle.

- Nickolas Lavidis is a Senior Lecturer and Researcher at the School of Biomedical Sciences, The University of Queensland. His research interest is environmental factors that influence neuronal plasticity. He is also interested in how stress influences reactive species, the nitrergic system and inflammation.

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