Input-dependent regulation of excitability controls dendritic maturation in somatosensory thalamocortical neurons

Laura Frangeul1, Vassilis Kehayas1, Jose V. Sanchez-Mut2, Sabine Fièvre1, K. Krishna-K1,3, Gabrielle Pouchelon1,4, Ludovic Telley1, Camilla Bellone1, Anthony Holtmaat1, Johannes Gräff2, Jeffrey D. Macklis5 & Denis Jabaudon1,6

Input from the sensory organs is required to pattern neurons into topographical maps during development. Dendritic complexity critically determines this patterning process; yet, how signals from the periphery act to control dendritic maturation is unclear. Here, using genetic and surgical manipulations of sensory input in mouse somatosensory thalamocortical neurons, we show that membrane excitability is a critical component of dendritic development. Using a combination of genetic approaches, we find that ablation of N-methyl-D-aspartate (NMDA) receptors during postnatal development leads to epigenetic repression of Kv1.1-type potassium channels, increased excitability, and impaired dendritic maturation. Lesions to whisker input pathways had similar effects. Overexpression of Kv1.1 was sufficient to enable dendritic maturation in the absence of sensory input. Thus, Kv1.1 acts to tune neuronal excitability and maintain it within a physiological range, allowing dendritic maturation to proceed. Together, these results reveal an input-dependent control over neuronal excitability and dendritic complexity in the development and plasticity of sensory pathways.
Neuronal morphology is critical to allow topographical mapping of the sensory periphery along input pathways. Regulation of dendritic complexity is particularly important in this process, as the expanse of the dendritic tree determines which subset of inputs a given neuron can respond to. During development, dendritic maturation and associated topographical mapping require appropriate input from the periphery [1–3]. For example, in the mouse somatosensory system, functional ablation of N-methyl-D-aspartate-NMDA receptors (NMDARs), which are normally activated by sensory input, leads to disrupted barrel map formation [4–8]. Similarly, severing the infraorbital nerve, which carries input from the whiskers, disrupts neuronal patterning at all relay stations of the whisker-to-cortex pathway [9,10]. Although both procedures disturb sensory mapping, the nature and specificity of the molecular/cellular processes at play in each of these conditions are poorly understood.

Somatosensory thalamocortical neurons of the ventroposterior medial nucleus (VPM) of the thalamus are well suited to study this question: they constitute a homogenous population of somatotopically organized neurons, which respond to whisker inputs and project to the primary somatosensory cortex [11]. During development, NMDARs are important for synaptic transmission at VPM neurons [12] and mosaic deletion of the NMDAR essential subunit Grin1 impairs synaptic maturation [8]. Likewise, functional elimination of trigeminothalamic synapses at VPM neurons is required for somatotopic refinement and is disturbed by sensory deprivation [13].

Using VPM neurons as a model population to study the input-dependent mechanisms underlying dendritic maturation, here we show that developmental genetic inactivation of NMDARs leads to an epigenetic repression of Kv1.1, a potassium channel regulating membrane excitability. As a result, NMDAR-lacking VPM neurons are hyperexcitable and display impaired dendritic maturation. Similarly, surgical disruption of whisker input by section of the infraorbital nerve leads to neuronal hyperexcitability and impaired dendritic maturation. Remarkably, overexpression of Kv1.1 is sufficient to enable dendritic development in both cases, revealing that neuronal excitability is a critical

**Fig. 1** NMDAR activation controls the dendritic maturation of VPM neurons during postnatal development. **a** Left: somatosensory thalamocortical neurons of the ventroposterior medial nucleus (VPM) of the thalamus respond to whisker inputs and project to the primary somatosensory cortex. Center: experimental time course and schematic representation of the labeling technique. Right: GFP+ neurons are visible in horizontal sections of the VPM in the 3rd ventricle. **b** Graphical mapping require appropriate input from the peripheral sensory periphery along input pathways. **c** Expression of Kv1.1 is sufficient to enable dendritic development in both cases, revealing that neuronal excitability is a critical
Fig. 2 Kcnal is a downstream target of NMDARs and controls neuronal excitability and dendritic maturation. a Illustrative microdissection of VPM nucleus at P1. VPM nucleus was identified by retrograde labeling from SI (green labeling). Red arrowheads show the microdissected specimen and its original location. Scale bar: 100 μm. b Top left: Kcnal expression is decreased in ThGrin1KO (n = 3). Red arrowheads show the labeling in VPM. Student’s t-test, *P < 0.05. Bottom left: in situ hybridization shows decreased Kcnal expression in ThGrin1KO VPM (n = 3). Scale bar: 200 μm. Right: Kcnal expression increases during development. c At P15, ThGrin1KO VPM neurons are hyperexcitable; this obviates the effects of the K+ channel blocker BaCl2. (Ctl n = 7, ThGrin1KO n = 4, Ctl + BaCl2 n = 5, ThGrin1KO + BaCl2 n = 5). One-way ANOVA with Tukey’s post-hoc test, **P < 0.01, ***P < 0.001; NS, not significant. d At P7, dendritic maturation is impaired by Kcnal down-regulation (P7 shKcnal n = 8 from 2 mice). P7 WT and P7 Grin1KOThEpMor data reported from Fig. 1b, d. Scale bar: 20 μm. e At P2, dendritic maturation is increased by overexpression of Kcnal (P2 KcnalGFP n = 14 from 4 mice). P2 WT and P7 WT data reported from Fig. 1b. Scale bar: 20 μm. WT, wild-type. One-way ANOVA with Tukey’s post-hoc test for all statistical tests relating to dendritic complexity, except for Sholl analyses for which a two-way ANOVA with Tukey’s post-hoc test was used. *P < 0.05, **P < 0.01, ***P < 0.001; NS, not significant.

Results

NMDAR controls the dendritic maturation of VPM neurons.

We characterized the dendritic development of VPM neurons during the first postnatal week in mice using in utero electroporation of a green fluorescent protein (GFP)-expressing plasmid to label individual neurons14 (Fig. 1a). This approach revealed an increase in dendritic complexity (as assessed by measuring the number of primary dendrites, branch points, and total dendritic length) between P2 and P7, a time at which whisker input becomes functional and pups experience their first extra-uterine stimuli (Fig. 1b, e, and Supplementary Figs. 1a, b and 2).

NMDARs have been implicated in neuronal patterning, and act in part through dendritic changes15–17. Suggesting that NMDARs also have a role in dendritic maturation in the VPM, we generated transgenic mice which lacked Grin1 in VPM neurons (and, to a lesser extent, in the posterior and lateral geniculate nuclei), by crossing SertCRE mice with Grin1loxFlox/fox mice (henceforth referred to as ThGrin1KO mice; Supplementary Figs. 3a, b). As previously reported, ThGrin1KO mice lacked whisker-specific patterning in the VPM (barreloids). This is similar to what is following neonatal infraorbital nerve section (IONS), which prevents input from the whiskers from reaching the hindbrain6, 9, 10 (Supplementary Fig. 3c).

We investigated the transcriptional targets of NMDARs by microdissecting VPM neurons in control and ThGrin1KO mice at P1, when dendrites are beginning to extend15 (Fig. 2a). Among differentially expressed genes, Kcnal stood out as being both regulated by NMDARs and developmentally regulated18 (i.e., significantly increased between P0 and P10, Student’s t-test; ***P < 0.001) (Fig. 2b, Supplementary Fig. 3d, and Supplementary Table 1).
The gene product of Kcnal1 is Kv1.1, a potassium channel that reduces dendritic excitability. As a consequence, decreased expression of Kcnal1 in ThGrinIKO VPM neurons should result in increased neuronal excitability. Confirming this prediction, whole-cell patch-clamp recording of ThGrinIKO VPM neurons in acute slices revealed an increase in spike numbers in response to depolarizing current injections, which was replicated by pharmacological blockade of K+ channels in wild-type VPM neurons (Fig. 2c, Supplementary Fig. 4, and Supplementary Table 2). Thus, developmental loss of NMDAR function leads to increased excitability of VPM neurons via decreased potassium conductances.

In retinal ganglion cells, Kv1.1 regulates the initial development of dendritic arbors through control of membrane excitability. To examine whether Kv1.1 likewise regulates dendritic complexity in VPM neurons, we downregulated Kcnal1 using in utero electroporation of a small hairpin RNA (shRNA). This led to impaired dendritic maturation with reduced complexity by P7, as we had observed following genetic ablation of NMDARs (Fig. 2d, and Supplementary Figs. 1d, i, 2, and 5). Supporting a role for Kcnal1 expression dynamics in the normal dendritic development of VPM neurons, early overexpression of this gene led to a developmental increase in dendritic complexity (Fig. 2e, and Supplementary Figs. 1e and 2). Together, these results suggest that Kcnal1, a downstream target of NMDARs, controls neuronal excitability and postnatal dendritic maturation.

NMDARs epigenetically regulate Kv1.1 via Gadd45b expression. We next investigated the molecular mechanism through which NMDARs regulate Kv1.1 expression. Gadd45b is an immediate early gene induced by NMDAR activation. Its gene product GADD45B is responsible for activity-induced DNA demethylation and associated gene de-repression in hippocampal neurons. We identified Gadd45b amongst the top genes that were down-regulated following loss of NMDARs in VPM neurons, suggesting that a similar pathway might be active in these neurons (Fig. 3a and Supplementary Table 1). Gadd45b−/− mice showed normal whisker patterning (Supplementary Fig. 6 and see Discussion). Using bisulphite pyrosequencing of Gadd45b+/− VPM neurons to identify changes in DNA methylation marks, we found an increase in the methylation of Kcnal1 promoter region (Fig. 3b). This epigenetic repression was associated with decreased expression of the Kcnal1 transcript, as demonstrated by in situ hybridization (ISH) (Fig. 3c). Consistent with this decreased expression of Kv1.1, Gadd45b−/− neurons were more excitable than their wild-type counterparts when challenged with depolarizing current injections (Fig. 3d). Thus, NMDARs regulate neuronal excitability via Gadd45b-mediated epigenetic de-repression of Kv1.1 (Fig. 3e).
We tested this model by performing IONS at birth to disrupt peripheral input to VPM neurons (VPMIONS) and examined how input deprivation affects neuronal excitability. As was the case with ThGrin1KO neurons, VPMIONS neurons displayed an increase in spiking at P15 when challenged with depolarizing current injections, which was occluded by blockade of K⁺ channels (Fig. 4a). As was the case in ThGrin1KO neurons, other electrophysiological parameters were not systematically affected by IONS (Supplementary Table 2). Neuronal hyperexcitability was already present at P7, in line with the early downregulation of Kv1.1 (Fig. 2b) and the developmental dynamics of the dendritic changes reported above (Supplementary Fig. 7 and Supplementary Table 3). Consistent with these findings, in vivo extracellular recordings at P20–23 revealed an increase in spike burstiness in VPM following IONS (Fig. 4b and Supplementary Fig. 8). As was the case in Grin1KOThEpor neurons, dendritic complexity was strongly decreased in VPMIONS neurons (Fig. 4c, and Supplementary Figs. 1f and 2). Together, these findings indicate that neuronal hyperexcitability is a critical determinant of abnormal dendritic development following genetic or surgical ablation of periphery-derived signals (Fig. 5c).

**Discussion**

Our findings unveil a functional pathway linking input-dependent DNA epigenetic modifications, neuronal excitability, and dendritic maturation during early postnatal development. We propose that during postnatal development, as peripheral sensory input increases, postsynaptic activation of NMDARs induces Kv1.1 expression, which homeostatically maintains VPM neuron responses within a physiological range. In contrast, when sensory input is lacking or impaired, Kv1.1 expression is decreased, leading to compensatory increased neuronal excitability. Although Kcnal1 expression levels have not been examined directly in Grin1KOThEpor neurons, overexpression of Kv1.1 restores the dendritic complexity of these cells to normal levels (Fig. 5a), supporting a downregulation of this transcript, as occurs in ThGrin1KO mice (e.g., Kcnal2 and Kcnal1, see Supplementary Table 1), which may act combinatorially with Kv channels to regulate excitability and dendritic maturation. Epigenetic...
regulation of this process has the advantage of allowing sustained transcriptional response even upon transient changes in the environment, thereby durably tuning neuronal excitability to fit external conditions as newborn mice start exploring their environment. Interestingly, GADD45B has also been associated with critical period plasticity in the visual cortex, where its expression is decreased by visual deprivation28. Therefore, regulation of this process has the advantage of allowing sustained plasticity in adult brain.

The persistence of barrels in Gadd45b−/− mice (Supplementary Fig. 6) and in a Kcnal−/− mouse29 suggests that competitive interactions between neurons may be at play during barrel patterning. Indeed, mosaic deletion approaches as performed here do not necessarily reflect the situation found in whole body knockouts (see, e.g., Datwani et al.20 vs. Mizuno et al.16 for differences between global and mosaic manipulations of Grin1 in L4 barrel neurons). Indeed, the former approach introduces a competitive advantage/disadvantage for manipulated cells, which is not the case in whole body knockouts, in which all cells are equally affected. Competition between manipulated and non-manipulated cells might be particularly relevant in studies of neuronal excitability, in which global neuronal silencing and local silencing have strikingly different effects (see, e.g., inter-ocular silencing have strikingly different effects (see, e.g., inter-ocular interactions during visual map development30; or effects of unilateral vs. bilateral silencing during callosal wiring31). In addition, regulatory mechanisms might come into play early in development to compensate for the missing gene in whole body knockouts, as both Gadd45b and Kv1.1 each belong to a family of structurally overlapping proteins.

Although VPM barreloid neurons and L4 barrel neurons belong to the same functional pathway, NMDAR activation appears to have a different effect on dendritic growth in these two cell types: loss of Grin1 increases dendritic length in L4 neurons20 but decreases it in VPM neurons (current study). These suggest that NMDARs can act on a variety of cellular differentiation programs and modulate features of neuronal development and circuit formation in a cell type-specific manner.
Although our study focuses on cell intrinsic electrophysiological changes in VPM neurons, synaptic input to these cells is likely also affected. Mosaic deletion of Grin1 in VPM neurons leads to decreased pruning ofafferent PrV axons, yet most of these inputs appear to be non-functional, as upregulation of AMPARs was disrupted at these synapses. Our findings are compatible with such a scenario, in that increased excitability following loss of input might allow loss of input. Similarly, changes in input to VPM neurons may also affect “top-down” afferents originating in the cortex. Although only little is known on the plasticity of these inputs following peripheral lesions, LSB input, which normally targets higher-order nuclei is functionally rewired onto visual thalamic neurons following enucleation, resulting in a new genetic identity of these cells. Whether a similar process is at play in the somatosensory system remains to be tested.

Neuronal hyperexcitability following IONS is somewhat surprising and may reflect denervation hypersensitivity secondary to loss of a critical input, as discussed above. An important consequence of this latter finding is that developmental lesions to whisker input pathways are not equivalent to the “silencing” downstream target neurons, as in fact such procedures result in hyperactive neurons. Similar processes may occur along other sensory pathways; we have for instance shown that assembly of inhibitory circuits within the dorsolateral geniculate nucleus, which relays input from the retina, is disrupted following developmental enucleation. Interestingly, secondary neuronal hyperactivity could be involved in maladaptive plasticity processes occurring following peripheral injuries, such as phantom limb pain.

Our results reveal that membrane hyperexcitability is a critical component of abnormal dendritic development following lesions to peripheral pathways and reducing neuronal excitability is sufficient to prevent the decrease in dendritic complexity observed following peripheral lesions. Importantly, although the mechanisms underlying hyperexcitability following genetic or surgical input manipulation may be distinct, they both result in impaired dendritic maturation and converge in being both restored by hyperpolarization. Given the tight link between input loss, hyperexcitability, and dendritic maturation reported here, it would be interesting to investigate neuronal silencing approaches to promote recovery of function following lesions to the central or peripheral nervous system.

Methods

Mice. C57Bl/6 male and female pups and adult mice were used. Transgenic mice consist in SerCre (B6.129(Cg)-Scl6a4tm(cre)Xaj/J, The Jackson Laboratory, stock number 014554). Grin1fllox (B6.129S4–Grin1tm2olj/J, The Jackson Laboratory, stock number 005246), A14 transgenic reporter mice (B6.Cg-Gf(Rosa26)Sor1aij, C3H/HeJ-Tumstatm(cre)Hao, The Jackson Laboratory, stock number 007914). Gadd45b inactivation was achieved using a mix of random hexamers—oligo d(T) primers and PrimerScript reverse transcriptase enzyme (Takara Bio Inc. Kit) following suppliers instructions. SYBR Green assays were designed using the program Primer Express v. 2.0 (Applied Biosystems) with default parameters. Amplicon sequences were aligned against the mouse genome by BLAST, to ensure that they were specific for the gene being tested. Oligonucleotides were obtained from Invitrogen.

For quantitative PCR, cDNA was synthesized from 1 μg of cDNA (from the second amplification) using a mix of random hexamers—oligo d(T) primers and PrimerScript reverse transcriptase enzyme (Takara Bio Inc. Kit) following suppliers instructions. SYBR Green assays were designed using the program Primer Express v. 2.0 (Applied Biosystems) with default parameters.

In utero electroporation. Timed pregnant C57Bl/6 or Grin1fllox mice with E12.5 embryos were anesthetized with isoflurane (4.5% induction, 2.5% during the surgery) and uterine horns were successively exposed after a midline laparotomy. Embryos were injected with 200 nl plasmid DNA solution (prepared in 0.9% NaCl, 0.3 mg/ml, Fast Green) into the third ventricle through the uterine wall. pCAG-IRESp2 (1 μg μl−1, gift from Guillermina López-Bendito) was injected alone or co-electroporated with a Kcnal1 shRNA (2 μg μl−1). Small hairpin (sh) RNA was purchased from Thermo Scientific (TRC Mouse Kcnal1 shRNA, RMM5434-EG16485). pCAG-CreFP2 was a gift from Connie Cepko (Addgene, plasmid 17376) and was injected in Grin1fllox embryos at 2.5 μg μl−1. pCAG-Kcnal1-ires-GFP was constructed by inserting the human Kcnal1 sequence (3 ligation, MH6278-202857646) into the pCAG-ires-GFP, pCAG-Kcnal1-ires-GFP was co-electroporated with a Kcnal1 shRNA (2 μg μl−1). Small hairpin (sh) RNA was purchased from Thermo Scientific (TRC Mouse Kcnal1 shRNA, RMM5434-EG16485). pCAG-CreFP2 was a gift from Connie Cepko (Addgene, plasmid 17376) and was injected in Grin1fllox embryos at 2.5 μg μl−1. pCAG-Kcnal1-ires-GFP was constructed by inserting the human Kcnal1 sequence (3 ligation, MH6278-202857646) into the pCAG-ires-GFP, pCAG-Kcnal1-ires-GFP was co-electroporated with a Kcnal1 shRNA (2 μg μl−1).

Histology. Postnatal mice were perfused with 4% paraformaldehyde (PFA) and brains were fixed overnight in 4% PFA at 4 °C. Fifty-micrometer vibratome sections (140 μm) were cut on a vibrating microtome (Leica, VT1000S) and were fixed overnight in 4% PFA at 4 °C. Fifty-micrometer vibratome sections (140 μm) were cut on a vibrating microtome (Leica, VT1000S) and were fixed overnight in 4% PFA at 4 °C. Fifty-micrometer vibratome sections (140 μm) were cut on a vibrating microtome (Leica, VT1000S) and were fixed overnight in 4% PFA at 4 °C.
For fluorescence immunohistochemistry, brain sections were incubated 1 h at room temperature in a blocking solution containing 3% bovine serum albumin and 0.3% Triton X-100 in PBS, and incubated overnight at 4°C with primary antibodies: guinea pig anti-VGLUT2 (1:2,000; Millipore, AB2251) and rabbit anti-GFP (1:1000; Invitrogen, A1122). Sections were rinsed three times in PBS and incubated 1 h at room temperature with the corresponding secondary antibodies (1:300).

For cytochrome oxidase staining, free-floating sections were placed in a solution of 0.5 mg/ml DAB, 0.5 mg/ml Cytochrome C (Sigma), 40 mg/ml sucrose, 0.1 mM Tris pH 7.6 at 37°C until staining appeared.

Imaging and quantification. All images were acquired on an Eclipse 90i fluorescence microscope (Nikon, Japan) or on a Zeiss LSM 700 Live confocal system (Carl Zeiss). Morphological quantifications were done blindly with respect to experimental conditions and one of the two investigators did the selection for location: no overlap with other labeled neurons; specifically, no overlap across primary dendrites.

Control P2 (n = 11 cells from 2 mice), control P7 (n = 10 cells from 2 mice), P7 Grin1KO+/− (n = 16 cells from 3 mice), P7 Grin1KO+/− + Kcnal2+/− (Kcnal2−/−) (n = 15 cells from 6 mice), P7 shKcnal1−/− (n = 8 cells from 2 mice), P7 shKcnal1−/− + Kcnal2−/− (Kcnal2−/−) (n = 13 cells from 4 mice), P2 Kcnal2−/− (n = 14 cells from 4 mice), P7 IONS (n = 10 cells from 2 mice), and P7 IONS + Kcnal2−/− (Kcnal2−/−) (n = 14 cells from 7 mice) VM neurons were reconstructed for quantitative analysis of neuronal dendritic arborization. In order to quantify changes in dendritic arborization, we quantified the number of primary dendrites, number of branch points, number of terminal point and total length. All values were normalized and expressed as a percentage of control P7 VM neurons values. Data are expressed as mean ± SEM and statistical analysis was performed with one-way analysis of variance (ANOVA) with Tukey’s post-hoc test with significance level set at P < 0.05.

In vivo extracellular electrophysiology. IONS mice (n = 12 - P20–23) and control mice (n = 4 - P20–21) of both sexes were obtained to use in vivo extracellular recordings. The animals were pretreated with glycopyrrolate (Robinal, 0.01 mg/kg, i.m., subcutaneously) at least 15 min before anesthesia, in order to prevent bradycardia and excessive salivation. Then, they were anesthetized with a mixture of medetomidin (Dorbene, 0.1 mg/kg−1), midazolam (Dormicin, 2.5 mg/kg−1), and fentanyl (Duragesic, 0.025 mg kg−1) in sterile NaCl 0.9%. Their head was shaved and depilatory cream (Veet) was applied. An incision was made to the skin and the skull was exposed. Lidocaine 1% was applied on the wound edges. Dental acrylic was applied before insertion of the stimulating electrode. Following the incision, a 25-gauge bent-tip electrode was inserted in the right corona radiata (at coordinates AP = –1.5, ML: 1.8) and connected to a multi-lead microelectrode array (MUA) (NeuroNexus). The stimulating electrode was connected to a 2-barrel micromanipulator, so that it could be positioned easily in the brain. Once the electrode was positioned in the caudate nucleus, a small incision was made in the skin to expose the electrode, and then it was positioned in the caudate nucleus. The stimulating electrode was inserted until it reached the target. The stimulating electrode was positioned in the left hemisphere. After the electrode was positioned in the correct location in the left hemisphere, the stimulating electrode was positioned in the right hemisphere. The electrodes were then fixed with dental acrylic.

In vitro electrophysiology. Mice were deeply anesthetized with isoflurane and were then decapitated. Brains were cut in cooled and oxygenated (95% O2, 5% CO2) artificial cerebrospinal fluid containing: 119 mM NaCl, 2.5 mM KCl, 1.3 mM MgCl2, 2.5 mM CaCl2, 1.0 mM Na2HPO4, 26.2 mM NaHCO3, and 11 mM glucose. Coronal slices containing the thalamus were kept at room temperature and were allowed to recover for at least 1 h before recording. The internal solution contained 140 mM potassium glutamate, 5 mM KCl, 10 mM HEPES, 0.2 mM EGTA, 2 mM MgCl2, 4 mM NaHATP, 0.3 mM NaGTP, and 10 mM sodium creatine phosphate. Currents were amplified (Multiclamp 700B, Axon Instruments), filtered at 5 kHz, and digitized at 20 kHz. One data point was used to determine the input resistance (Input impedance). The liquid junction potential was +12 mV. Spike measurements for a given cell are the mean values measured from one to three cycles of current steps (500 ms duration at 0.1 Hz, 0 to + 400 pA range with a 50 pA step increment). For Figs. 3c and 4a, −P5 control, ThGrin1KO and IONS mice were used. The K+ -channel blocker BaCl2 (1 mM) was bath-applied. For Fig. 4d, P5 control and Gadd45β−/− mice were used. For Supplementary Fig. 6a, P7 control, IONS, and IONS + Kcnal2−/− mice were used. Data are expressed as mean ± SEM and statistical significance was determined by one-way ANOVA with Tukey’s post-hoc test with significance level set at P < 0.05.
**Statistical analysis.** No statistics were used to determine group sample size; however, sample sizes were similar to those used in previous publications from our group and others. No randomization was performed. Tests were performed assuming equal variances except when indicated. n-values refer to cell numbers unless specified otherwise. Values are represented as means ± SEM throughout the manuscript. p-values: NS, not significant (P > 0.05), *P < 0.05, **P < 0.01, ***P < 0.001.

**Data availability.** All relevant data are available from the authors.

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**Author contributions**

D.J. and I.D.M. conceived the initial project. L.F. designed the experimental layout and scientific model, and wrote the manuscript with help from D.J. and other authors. L.F., V. K., J.V.S.-M., S.F., K.K.-K., G.P., and C.B. performed experiments and analyses. L.T.
helped with data analyses. D.J., J.D.M., A.H., and J.G. advised on experiments and manuscript preparation.

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