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1 **Lactate is an energy substrate for rodent cortical neurons and enhances their**
2 **firing activity.**

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28 **Summary**

29 Glucose is the mandatory fuel for the brain, yet the relative contribution of glucose
30 and lactate for neuronal energy metabolism is unclear. We found that increased
31 lactate, but not glucose concentration, enhances the spiking activity of neurons of the
32 cerebral cortex. Enhanced spiking was dependent on ATP-sensitive potassium (K_{ATP})
33 channels formed with KCNJ11 and ABCC8 subunits, which we show are functionally
34 expressed in most neocortical neuronal types. We also demonstrate the ability of
35 cortical neurons to take-up and metabolize lactate. We further reveal that ATP is
36 produced by cortical neurons largely via oxidative phosphorylation and only modestly
37 by glycolysis. Our data demonstrate that in active neurons, lactate is preferred to
38 glucose as an energy substrate, and that lactate metabolism shapes neuronal activity
39 in the neocortex through K_{ATP} channels. Our results highlight the importance of
40 metabolic crosstalk between neurons and astrocytes for brain function.

41

42 **Impact Statement**

43 Lactate is preferred to glucose as an energy substrate and exacerbates spiking
44 activity in most neuron types of juvenile somatosensory cortex by closing ATP-
45 sensitive potassium channels.

46

47 **Keywords**

48 K_{ATP} channel, pyramidal cell, interneuron, glucose, single cell RT-PCR, ATP.

49

50 **Highlights**

- 51
- 52 • Most cortical neuron subtypes express functional K_{ATP} channels.
 - 53 • Lactate enhances spiking activity via its uptake and closure of K_{ATP} channels.
 - 54 • Cortical neurons take up and oxidize lactate.
 - 55 • Cortical neurons produce ATP mainly by oxidative phosphorylation.
- 56
- 57

58 **Introduction**

59 The human brain represents 2% of the body mass, yet it consumes about 20% of
60 blood oxygen and glucose which are mandatory energy substrates (Clarke and
61 Sokoloff, 1999). The majority (~50-80%) of the cerebral energy metabolism is
62 believed to be consumed by the Na⁺/K⁺ ATPase pump to maintain cellular ionic
63 gradients dissipated during synaptic transmission and action potentials (Attwell and
64 Laughlin, 2001;Lennie, 2003). Synaptic and spiking activities are also coupled with
65 local cerebral blood flow and glucose uptake (Devor et al., 2008;Logothetis, 2008).
66 This process, referred to as neurovascular and neurometabolic coupling, is the
67 physiological basis of brain imaging techniques (Raichle and Mintun, 2006) and
68 maintains extracellular glucose within a physiological range of 2-3 mM (Silver and
69 Erecinska, 1994;Hu and Wilson, 1997b). Also, following increased neuronal activity
70 extracellular lactate increases (Prichard et al., 1991;Hu and Wilson, 1997a) for
71 several minutes up to twice of its 2-5 mM basal concentration despite oxygen
72 availability (Magistretti and Allaman, 2018).

73

74 Based on the observations that various by-products released during glutamatergic
75 transmission stimulate astrocyte glucose uptake, aerobic glycolysis and lactate
76 release (Pellerin and Magistretti, 1994;Voutsinos-Porche et al., 2003;Ruminot et al.,
77 2011;Choi et al., 2012;Sotelo-Hitschfeld et al., 2015;Lerchundi et al., 2015), lactate
78 has been proposed to be shuttled from astrocytes to neurons to meet neuronal
79 energy needs. This hypothesis is supported by the existence of a lactate gradient
80 between astrocytes and neurons (Machler et al., 2016), the preferential use of lactate
81 as an energy substrate in cultured neurons (Bouzier-Sore et al., 2003;Bouzier-Sore
82 et al., 2006), and its ability to support neuronal activity during glucose shortage
83 (Schurr et al., 1988;Rouach et al., 2008;Wyss et al., 2011;Choi et al., 2012).
84 However, the use of different fluorescent glucose analogues to determine whether
85 astrocytes or neurons take up more glucose during sensory-evoked neuronal activity
86 has led to contradicting results (Chuquet et al., 2010;Lundgaard et al., 2015).
87 Furthermore brain slices and *in vivo* evidence have indicated that synaptic and
88 sensory stimulation enhanced neuronal glycolysis and potentially lactate release by
89 neurons (Ivanov et al., 2014;Diaz-Garcia et al., 2017), thereby challenging the
90 astrocyte-neuron lactate shuttle hypothesis. Hence, the relative contribution of
91 glucose and lactate to neuronal ATP synthesis remains unresolved.

92 ATP-sensitive potassium channels (K_{ATP}) act as metabolic sensors controlling
93 various cellular functions (Babenko et al., 1998). Their open probability (P_o) is
94 regulated by the energy charge of the cell (*i.e.* the ATP/ADP ratio). While ATP
95 mediates a tonic background inhibition of K_{ATP} channels, cytosolic increases of ADP
96 concentrations that occur as a sequel to enhanced energy demands, increase the P_o
97 of K_{ATP} channels. In neurons, electrical activity is accompanied by enhanced sodium
98 influx, which in turn activates the Na^+/K^+ ATPase. Activity of this pump alters the
99 submembrane ATP/ADP ratio sufficiently to activate K_{ATP} channels (Tanner et al.,
100 2011). The use of fluorescent ATP/ADP biosensors has demonstrated that K_{ATP}
101 channels are activated ($P_o > 0.1$) when ATP/ADP ratio is ≤ 5 (Tantama et al., 2013).

102
103 K_{ATP} channels are heterooctamers composed of four inwardly rectifying K^+ channel
104 subunits, KCNJ8 (previously known as Kir6.1) or KCNJ11 (previously known as
105 Kir6.2), and four sulfonylurea receptors, ABCC8 (previously known as SUR1) or
106 ABCC9 (previously known as SUR2), the later existing in two splice variants (SUR2A
107 and SUR2B) (Sakura et al., 1995; Aguilar-Bryan et al., 1995; Inagaki et al.,
108 1995b; Isomoto et al., 1996; Inagaki et al., 1996; Chutkow et al., 1996; Yamada et al.,
109 1997; Li et al., 2017; Martin et al., 2017; Lee et al., 2017; Puljung, 2018). The
110 composition in K_{ATP} channel subunits confers different functional properties,
111 pharmacological profiles as well as metabolic sensitivities (Isomoto et al.,
112 1996; Inagaki et al., 1996; Gribble et al., 1997; Yamada et al., 1997; Okuyama et al.,
113 1998; Liss et al., 1999). K_{ATP} channel subunits are expressed in the neocortex
114 (Ashford et al., 1988; Karschin et al., 1997; Dunn-Meynell et al., 1998; Thomzig et al.,
115 2005; Cahoy et al., 2008; Zeisel et al., 2015; Tasic et al., 2016) and have been shown
116 to protect cortical neurons from ischemic injury (Heron-Milhavet et al., 2004; Sun et
117 al., 2006) and to modulate their excitability (Gimenez-Cassina et al., 2012) and
118 intrinsic firing activity (Lemak et al., 2014). K_{ATP} channels could thus be leveraged to
119 decipher electrophysiologically the relative contribution of glucose and lactate to
120 neuronal ATP synthesis. Here, we apply single-cell RT-PCR (scRT-PCR) to identify
121 the mRNA subunit composition of K_{ATP} channel across different neocortical neuron
122 subtypes and demonstrate lactate as the preferred energy substrate that also
123 enhances firing activity.

124

125

126 **Results**

127 **Expression of K_{ATP} channel subunits in identified cortical neurons**

128 We first sought to determine whether K_{ATP} channel subunits were expressed in
129 different neuronal subtypes from the neocortex. Neurons (n=277) of the juvenile rat
130 barrel cortex from layers I to IV (Supplementary file 1) were functionally and
131 molecularly characterized in acute slices by scRT-PCR (Figure 1), whose sensitivity
132 was validated from 500 pg of total cortical RNAs (Figure 1-figure supplement 1A).
133 Neurons were segregated into 7 different subtypes according to their overall
134 molecular and electrophysiological similarity (Figure 1A) using unsupervised Ward's
135 clustering (Ward, 1963), an approach we previously successfully used to classify
136 cortical neurons (Cauli et al., 2000; Gallopin et al., 2006; Karagiannis et al., 2009).
137 Regular spiking (RS, n=63) and intrinsically bursting (IB, n=10) cells exhibited the
138 molecular characteristics of glutamatergic neurons, with very high single-cell
139 detection rate (n=69 of 73, 95%) of vesicular glutamate transporter 1 (*Slc17a7*) and
140 low detection rate (n=7 of 73, 10%) of glutamic acid decarboxylases (*Gad6*, Figure
141 1B-E and Supplementary file 2), the GABA synthesizing enzymes. This group of
142 glutamatergic neurons distinctly displayed hyperpolarized resting membrane potential
143 (-81.2 ± 0.8 mV), possessed a large membrane capacitance (108.6 ± 3.6 pF),
144 discharged with wide action potentials (1.4 ± 0.0 ms) followed by medium
145 afterhyperpolarizations (mAHs). These neurons did sustain only low maximal
146 frequencies (35.4 ± 1.6 Hz) and showed complex spike amplitude accommodation
147 (Supplementary file 5). In contrast to RS neurons, IB neurons were more prominent
148 in deeper layers (Supplementary file 1) and their bursting activity affected their
149 adaptation amplitudes and kinetics (Figure 1C and Supplementary files 4,5), spike
150 broadening (Figure 1C and Supplementary file 6) and the shape of mAHs (Figure 1C
151 and Supplementary file 7).

152 All other neuronal subtypes were characterized by a high single-cell detection rate of
153 *Gad2* and/or *Gad1* mRNA (n=202 of 204, 99%, Figure 1B and Supplementary file 2)
154 and therefore likely corresponded to GABAergic interneurons. Among *Gad*-positive
155 population, neurons were frequently positive for vasoactive intestinal polypeptide
156 (*Vip*) mRNA, and in accordance to their electrophysiological phenotypes, were
157 segregated into Bursting *Vip* (n=27) and Adapting *Vip* (n=59) neurons. These *Vip*
158 interneurons were further characterized by high membrane resistance (581 ± 27 MΩ)

159 and small membrane capacitance (52.7 ± 2.3 pF, Figure 1B-C and Supplementary
160 file 3).

161 In other GABAergic interneurons somatostatin (*Sst*) and calbindin (*Calb1*) as well as
162 neuropeptide Y (*Npy*) to a lesser extent, were frequently detected and functionally
163 corresponded to Adapting *Sst* neurons (n=24, Figure 1B and Supplementary file 2).
164 They displayed depolarized resting membrane potential, pronounced voltage sags,
165 low rheobases and pronounced afterdepolarizations (Figure 1C and Supplementary
166 files 3-4,7). In another group of GABAergic adapting interneurons located in
167 superficial layers, mRNA for *Npy* was detected at a high rate (n=31 of 56, 55%). In
168 these Adapting NPY interneurons mRNA for nitric oxide synthase-1 (*Nos1*) was
169 detected at a lower rate (Figure 1B and Supplementary files 1,2). In response to
170 suprathreshold depolarizing current steps, these interneurons showed very little spike
171 frequency adaptation (Figure 1C and Supplementary file 4). Finally, parvalbumin
172 (*Pvalb*) was observed in virtually all neurons of a subpopulation termed Fast Spiking-
173 *Pvalb* interneurons (FS-*Pvalb*, n=37 of 38, 97%, Figure 1B and Supplementary file 2).
174 In comparison to all other cortical neurons described above, they were characterized
175 by low membrane resistance (201 ± 13 M Ω), fast time constant, high rheobase, very
176 short spikes (0.6 ± 0.0 ms) with sharp fast afterhyperpolarizations (fAHs) and the
177 ability to sustain high firing rates (139.9 ± 6.8 Hz) with little to no frequency
178 adaptation (Figure 1C and Supplementary files 3-7). These data thus identified
179 different neuronal subtypes based on their distinctive electrophysiological and
180 molecular features (Ascoli et al., 2008) confirming our previous classification
181 schemes (Cauli et al., 2000; Gallopin et al., 2006; Karagiannis et al., 2009).

182 The functional and molecular classification of cortical neurons allowed us to probe for
183 the single-cell expression of mRNA for K_{ATP} channel subunits (Figure 1-figure
184 supplement 1A) in well defined subpopulations. Apart from a single Adapting *Npy*
185 neuron (Figure 1D), where *Kcnj8* mRNA was observed, only the *Kcnj11* and *Abcc8*
186 subunits were detected in cortical neurons (in 25%, n=63 of 248 neurons; and in
187 10%, n=28 of 277 of neurons; respectively). The single-cell detection rate was similar
188 between the different neuronal subtypes (Figure 1F). We also codetected *Kcnj11* and
189 *Abcc8* in cortical neurons (n=14 of 248, Figure 1D) suggesting the expression of
190 functional K_{ATP} channels.

191

192 **Characterization of K_{ATP} channels in cortical neurons**

193 To assess functional expression of K_{ATP} channels in identified cortical neurons ($n=18$,
194 Figure 2A), we measured the effects of different K_{ATP} channel modulators on whole-
195 cell currents ($Q_{(3,18)}=32.665$, $p=3.8 \times 10^{-7}$, Friedman test) and membrane resistances
196 ($Q_{(3,18)}=40.933$, $p=6.8 \times 10^{-9}$). Pinacidil (100 μ M), an ABCC9-preferring K_{ATP} channel
197 opener (Inagaki et al., 1996;Moreau et al., 2005), had little or no effect on current (4.1
198 ± 3.7 pA, $p=0.478$) and membrane resistance (-9.6 ± 3.7 %, $p=0.121$, Figure 2B-C).
199 By contrast, diazoxide (300 μ M), an opener acting on ABCC8 and SUR2B-containing
200 K_{ATP} channels (Inagaki et al., 1996;Moreau et al., 2005), consistently induced an
201 outward current (45.0 ± 9.6 pA, $p=4.8 \times 10^{-5}$) and a decrease in membrane
202 resistance ($-34.5 \pm 4.3\%$, $p=3.6 \times 10^{-5}$) indicative of the activation of a hyperpolarizing
203 conductance (Figure 2B-C). The sulfonylurea tolbutamide (500 μ M, Figure 2B-C), a
204 K_{ATP} channel blocker (Ammala et al., 1996;Isomoto et al., 1996;Gribble et al.,
205 1997;Isomoto and Kurachi, 1997), did not change whole-cell basal current (-6.6 ± 3.0
206 pA, $p=0.156$) or membrane resistance ($20.5 \pm 7.5\%$, $p=3.89 \times 10^{-2}$). Conversely,
207 tolbutamide dramatically reversed diazoxide effects on both current ($p=4.1 \times 10^{-8}$)
208 and membrane resistance ($p=5.8 \times 10^{-10}$).

209 All pharmacologically analyzed neurons ($n=63$) exhibited a more positive whole-cell
210 current ($\Delta I=53 \pm 6$ pA, range: 4 to 228 pA) and a lower membrane resistance ($\Delta R_m=-$
211 270 ± 31 M Ω , range: -17 to -1221 M Ω) under diazoxide than under tolbutamide,
212 indicative of their sensitivity to K_{ATP} channel manipulation. In virtually all neuronal
213 subtypes ($H_{(6,43)}=2.274$, $p=0.810$, Kruskal–Wallis H test) or groups ($t_{(42)}=0.3395$,
214 $p=0.736$, Student's t-test), the diazoxide-tolbutamide current/voltage relationship
215 reversed very close to the theoretical potassium equilibrium potential ($E_K=-106.0$ mV,
216 Figure 2D-F) confirming the opening of a selective potassium conductance. Besides
217 its effects on plasma membrane K_{ATP} channels, diazoxide is also a mitochondrial
218 uncoupler (Drose et al., 2006) which increases reactive oxygen species (ROS)
219 production. This might stimulate Ca^{2+} sparks and large-conductance Ca^{2+} -activated
220 potassium channels (Xi et al., 2005) leading to potential confounding effects. This
221 possibility was ruled out by the observation that Mn(III)tetrakis(1-methyl-4-
222 pyridyl)porphyrin (MnTMPyP, 25 μ M), a ROS scavenger (D'Agostino et al., 2007), did
223 not reduce the diazoxide-tolbutamide responses on current ($t_{(10)}=0.76559$, $p=0.462$,
224 Figure 2-figure supplement 1A,B) and conductance ($t_{(10)}=1.24758$, $p=0.241$, Figure 2-
225 figure supplement 1A,C).

226 Cortical neurons exhibited K_{ATP} conductances of similar value between their subtypes
227 ($H_{(6,63)}=5.6141$, $p=0.468$) or groups ($U_{(9,54)}=233$, $p=0.855$, Mann–Whitney U test,
228 Figures S3A,B). K_{ATP} channels activated by diazoxide essentially doubled the whole
229 cell conductance in the subthreshold membrane potential compared to control or
230 tolbutamide conditions, regardless of neuronal subtypes ($H_{(6,63)}=5.4763$, $p=0.484$) or
231 groups ($t_{(61)}=1.324$, $p=0.191$, Figures 2G,H). Also, K_{ATP} current density was similar
232 ($H_{(6,63)}=4.4769$, $p=0.612$, $U_{(9,54)}=240.5$, $p=0.965$, Figure 2-figure supplement 2C,D).
233 Twenty nine diazoxide/tolbutamide-responsive neurons were successfully
234 characterized by scRT-PCR. *Kcnj11* and *Abcc8* mRNAs were detected in 35% ($n=10$
235 of 29) and 7% ($n=2$ of 29) of these neurons, respectively. These proportions are low
236 compared to the pharmacological responsiveness but similar to the whole sample of
237 profiled cortical neurons ($p=0.3721$ and $p=1.0000$, Fisher's exact test). These
238 observations suggest that *Kcnj11* and *Abcc8* subunits were underdetected by scRT-
239 PCR mRNA profiling. Together with the pinacidil unresponsiveness and the lack of
240 *Abcc9* detection, these data indicate that the large majority of cortical neurons
241 express functional ABCC8-mediated K_{ATP} channels across different subpopulations.
242 To confirm that KCNJ11 is the pore-forming subunit of K_{ATP} channels in cortical
243 neurons, we used a genetic approach based on *Kcnj11* knock-out mice (Miki et al.,
244 1998). We first verified that *Kcnj11* and *Abcc8* subunits can be detected in pyramidal
245 cells from wild type mice by scRT-PCR (Figure 3A,B). We next used a dialysis
246 approach by recording neurons with an ATP-free pipette solution (Miki et al., 2001)
247 enriched in sodium (20 mM) to stimulate submembrane ATP depletion and ADP
248 production by the Na^+/K^+ ATPase, which is known to activate K_{ATP} channels (Figure
249 3H). We confirmed that *Atp1a1* and *Atp1a3* (Figure 3B) were the main α -subunits of
250 the Na^+/K^+ ATPase pump detected in pyramidal neurons (Zeisel et al., 2015; Tasic et
251 al., 2016). Dialysis of ATP-free/20 mM Na^+ -pipette solution induced an outward
252 current in most *Kcnj11*^{+/+} neurons recorded ($n=19$ out of 26; mean for $n=26$: $46.7 \pm$
253 19.0 pA at -50 mV, median value= 16.2 pA, $Chi^2=5.538$, $p=0.01860$, one sample
254 median test). In some neurons ($n=6$ of 26), this procedure resulted in an outward
255 current of more than 100 pA that reversed close to E_K (see example in Figure 3C,E).
256 In contrast, this current was not observed in *Kcnj11*^{-/-} neurons ($U_{(26,22)}=78$, $p=2.4221$
257 $\times 10^{-6}$, one-tailed, Figure 3D-G). Instead, dialysis induced an inward current in most
258 *Kcnj11*^{-/-} neurons ($n=20$ of 22; mean for $n=22$: -59.9 ± 11.9 pA, $n=22$, median value= $-$
259 61.9 pA, $Chi^2=14.727$, $p=0.000124$, one sample median test), suggesting that other

260 conductances than the K_{ATP} channels were also altered. Collectively, these data
261 indicate that cortical neurons predominantly express functional K_{ATP} channels
262 composed of KCNJ11 and ABCC8 subunits.

263

264 **Modulation of neuronal excitability and activity by K_{ATP} channel**

265 Despite their large diversity, cortical neurons display a widespread functional
266 expression of K_{ATP} channels, questioning how these channels integrate the metabolic
267 environment to adjust neuronal activity. To address this question, we first evaluated
268 in identified cortical neurons ($n=39$) the ability of K_{ATP} channels to modulate neuronal
269 excitability, notably by measuring membrane potentials ($Q_{(2,39)}=38.000$, $p=5.6 \times 10^{-9}$)
270 and membrane resistances ($Q_{(2,39)}=40.205$, $p=1.9 \times 10^{-9}$), as well as spiking activity
271 ($Q_{(2,39)}=28.593$, $p=6.2 \times 10^{-7}$). Following electrophysiological identification, the K_{ATP}
272 channel blocker tolbutamide was applied, which resulted in a slight depolarization
273 ($\Delta V_m=2.6 \pm 0.8$ mV, $p=1.74 \times 10^{-2}$, Figure 4A,D) and increase in membrane
274 resistance ($\Delta R_m=78 \pm 32$ M Ω , $p=1.52 \times 10^{-3}$, Figure 4B,E). These effects were strong
275 enough to trigger and stimulate the firing of action potentials ($\Delta F=0.3 \pm 0.2$ Hz, $p=$
276 9.21×10^{-3} , Figure 4A,C,F). By contrast, diazoxide hyperpolarized cortical neurons ($-$
277 4.0 ± 0.6 mV, $p=1.87 \times 10^{-4}$, Figure 4A,D), decreased their membrane resistance (-39
278 ± 23 M Ω , $p=1.52 \times 10^{-3}$, Figure 4B,E) but did alter their rather silent basal spiking
279 activity (-0.1 ± 0.1 Hz, $p=0.821$, Figure 4A,C,F).

280 Most cortical neurons ($n=32$ of 39) showed modulation of neuronal excitability by
281 both K_{ATP} channel modulators and were considered to be responsive. A similar
282 proportion of responsive neurons was observed between neuronal subtypes (Figure
283 4-figure supplement 1A, $\text{Chi}^2_{(5)}=7.313$, $p=0.1984$) or groups (Figure 4-figure
284 supplement 1B, $p=0.9999$, Fisher's exact test). The apparent relative lack of
285 responsiveness in FS-*Pvalb* interneurons (Figure 4-figure supplement 1A), despite a
286 whole-cell K_{ATP} conductance similar to that of other neuronal types (Figure 2-figure
287 supplement 2A), is likely attributable to their low input resistance (Supplementary file
288 3) making K_{ATP} channels less effective to change membrane potential. Overall, K_{ATP}
289 channels modulated membrane potential, resistance and firing rate by up to 7.9 ± 0.9
290 mV, $76 \pm 17\%$ and 0.5 ± 0.2 Hz, respectively. This modulation of neuronal excitability
291 (Figure 4G-J) and activity (Figure 4-figure supplement 1C,D) was similar between
292 neuronal subtypes or groups (Figure 4H-J and Figure 4-figure supplement 1C-E).

293 Thus, K_{ATP} channels modulate the excitability and activity of all subtypes of cortical
294 neurons.

295

296 **Enhancement of neuronal activity by lactate via modulation of K_{ATP} channels**

297 The expression of metabolically sensitive K_{ATP} channels by cortical neurons suggests
298 their ability to couple the local glycolysis capacity of astrocytes with spiking activity.
299 We therefore evaluated whether extracellular changes in glucose and lactate could
300 differentially shape the spiking activity of cortical neurons through their energy
301 metabolism and K_{ATP} channel modulation. Importantly, to preserve intracellular
302 metabolism, neurons were recorded in perforated patch-configuration. Stable firing
303 rates of about 4 Hz inducing ATP consumption by the Na^+/K^+ ATPase (Attwell and
304 Laughlin, 2001) were evoked by applying a depolarizing current and continuously
305 monitored throughout changes in extracellular medium (Figure 5A, $Q_{(2,16)}=22.625$,
306 $p=1.222 \times 10^{-5}$).

307 Decreasing extracellular glucose from 10 mM to a normoglycemic concentration of
308 2.5 mM (Silver and Erecinska, 1994;Hu and Wilson, 1997b) did not change firing rate
309 (Figure 5A,B, $p=0.2159$) of cortical neurons ($n=16$). By contrast, supplementing
310 extracellular 2.5 mM glucose with 15 mM lactate, an isoenergetic condition to 10 mM
311 glucose for having the same number of carbon atoms, roughly doubled the firing rate
312 compared to both 2.5 ($p=7.829 \times 10^{-4}$) and 10 mM glucose ($p=4.303 \times 10^{-6}$)
313 conditions. Firing rate enhancement by lactate was dose-dependent ($H_{(7,76)}=35.142$,
314 $p=1.052 \times 10^{-5}$) and reached statistical significance above 5 mM (Figure 5C). We
315 reasoned that this effect could be mediated by K_{ATP} channel closure. Indeed, the
316 increase in firing rate by lactate (209 ± 49 %) was strongly reduced by the K_{ATP}
317 channel activator diazoxide (71 ± 18 %, $p=3.346 \times 10^{-3}$, Figure 5D). Tolbutamide
318 reversed diazoxide's effect (160 ± 17 %, $p=9.345 \times 10^{-3}$) but did not increase firing
319 rate further ($p=0.5076$). This occlusion of tolbutamide's effect by 15 mM lactate also
320 suggests that this concentration reaches saturating levels and is the highest
321 metabolic state that can be sensed by K_{ATP} channels. Enhancement of neuronal
322 activity by lactate was also observed in *Kcnj11*^{+/+} cortical neurons (147 ± 25 %, $p=2.840 \times 10^{-2}$)
323 but not in *Kcnj11*^{-/-} mice (112 ± 32 %, $p=0.8785$, Figure 5E). These
324 observations indicate that lactate enhances neuronal activity via a closure of K_{ATP}
325 channels (Figure 5F).

326

327 **Mechanism of lactate-sensing**

328 To determine whether lactate-sensing involves intracellular lactate oxidative
329 metabolism and/or extracellular activation of the lactate receptor GPR81, we next
330 probed the expression of monocarboxylate transporters (MCTs), which allow lactate
331 uptake. Consistent with mouse mRNAseq data (Zeisel et al., 2015;Tasic et al., 2016),
332 *Slc16a1* (previously known as MCT1) and *Slc16a7* (previously known as MCT2)
333 were the main transporters detected in rat cortical neurons, although with relatively
334 low single cell detection rates (54 of 277, 19.5% and 78 of 277, 28.2%, for *Slc16a1*
335 and *Slc16a7*, respectively, Figure 6A and Figure 6-figure supplement 1).

336 The expression of monocarboxylate transporters in cortical neurons is compatible
337 with lactate uptake and metabolism leading to the closure of K_{ATP} channels and an
338 increase in firing rate. We thus evaluated whether lactate uptake was needed for
339 lactate-sensing. We used 250 μ M α -cyano-4-hydroxycinnamic acid (4-CIN), a
340 concentration blocking lactate uptake while only moderately altering mitochondrial
341 pyruvate carrier in brain slices (Schurr et al., 1999;Ogawa et al., 2005;Galeffi et al.,
342 2007). 4-CIN reversed the increased firing rate induced by lactate (Figure 6B, $T(9)=0$,
343 $p=7.686 \times 10^{-3}$) indicating that facilitated lactate transport is required for K_{ATP} channel
344 closure and in turn firing rate acceleration.

345 A mechanism of lactate-sensing involving an intracellular lactate oxidative
346 metabolism would also require the expression of lactate dehydrogenase (LDH), that
347 reversibly converts lactate and nicotinamide adenine dinucleotide (NAD^+) to pyruvate
348 and NADH (Figure 6E, inset). We thus also probed for the expression of *Ldh*
349 subunits. *Ldha* and *Ldhb* were observed in a large majority of cortical neurons with
350 *Ldha* being more frequent in glutamatergic neurons than in GABAergic interneurons
351 ($p=1.61 \times 10^{-2}$, Figure 6A and Figure 6-figure supplement 1). Nonetheless, neuron
352 subtypes analysis did not allow to disclose which populations express less frequently
353 *Ldha*. (Figure 6-figure supplement 1). To confirm the ability of cortical neurons to take
354 up and oxidize lactate we also visualized NADH fluorescence dynamics (Chance et
355 al., 1962) induced by bath application of lactate. Widefield somatic NADH
356 fluorescence appeared as a diffuse labeling surrounding presumptive nuclei (Figure
357 6D). Consistent with lactate transport by MCTs and oxidization by LDH, NADH was
358 increased under lactate application ($U_{(61,67)}=196$, $p=3.1 \times 10^{-24}$, Figure 6E-F).

359 Since the lactate receptor GPR81 has been observed in the cerebral cortex
360 (Lauritzen et al., 2014), lactate-sensing might also involve this receptor. This

361 possibility was ruled out by the observation that pyruvate (15 mM), which is
362 transported by MCTs (Broer et al., 1998;Broer et al., 1999) but does not activate
363 GPR81 (Ahmed et al., 2010), enhanced firing rate to an extent similar to that of
364 lactate (Figure 6C, $U_{(16,6)}=43$, $p=0.7468$). In line with its uptake and reduction,
365 pyruvate also decreased NADH (Figure 6E-F, $U_{(44,67)}=868$, $p=2.08 \times 10^{-4}$).
366 The requirement of monocarboxylate transport and the similar effect of lactate and
367 pyruvate on neuronal activity suggest that once taken up, lactate would be oxidized
368 into pyruvate and metabolized by mitochondria to produce ATP, leading in turn to a
369 closure of K_{ATP} channels and increased firing rate. The apparent absence of glucose
370 responsiveness in cortical neurons also suggests that glycolysis contributes modestly
371 to ATP production. To determine the relative contribution of glycolysis and oxidative
372 phosphorylation to ATP synthesis, we transduced the genetically encoded
373 fluorescence resonance energy transfer (FRET)-based ATP biosensor AT1.03^{YEMK}
374 (Imamura et al., 2009) using a recombinant Sindbis virus. AT1.03^{YEMK} fluorescence
375 was mostly observed in pyramidal shaped cells (Figure 6G), consistent with the
376 strong tropism of this viral vector towards pyramidal neurons (Piquet et al., 2018).
377 Blocking glycolysis with 200 μ M iodoacetic acid (IAA) decreased modestly the FRET
378 ratio by $2.9 \pm 0.2\%$ (Figure 6H, $p=2.44 \times 10^{-13}$). By contrast, adding potassium
379 cyanide (KCN, 1mM), a respiratory chain blocker, reduced the FRET ratio to a much
380 larger extent ($52.3 \pm 0.6\%$, Figure 6H, $p=2.44 \times 10^{-13}$). KCN also induced a strong
381 NADH fluorescence increase (Figure 6-figure supplement 2A-B, $U_{(12,42)}=0$, $p=5.83 \times$
382 10^{-12}), indicating a highly active oxidative phosphorylation in cortical neurons.
383

384 **Discussion**

385 We report that in juvenile rodents extracellular lactate and pyruvate, but not glucose,
386 enhance the activity of cortical neurons through a mechanism involving facilitated
387 transport and the subsequent closure of K_{ATP} channels composed of KCNJ11 and
388 ABCC8 subunits. ATP synthesis derives mostly from oxidative phosphorylation and
389 weakly from glycolysis in cortical neurons. Together with their ability to oxidize lactate
390 by LDH, these observations suggest that lactate is a preferred energy substrate over
391 glucose in cortical neurons. Besides its metabolic importance lactate also appears as
392 a signaling molecule enhancing firing activity (Figure 7). This suggests that an
393 efficient neurovascular and neurometabolic coupling could define a time window of
394 an up state of lactate during which neuronal activity and plasticity would be locally
395 enhanced (Suzuki et al., 2011; Jimenez-Blasco et al., 2020).

396

397 **K_{ATP} channel subunits in cortical neurons**

398 Similarly to neurons of the hippocampal formation (Zawar et al., 1999; Cunningham et
399 al., 2006; Sada et al., 2015) we found that, regardless of the neuronal type, most
400 neocortical neurons express diazoxide-sensitive, but pinacidil-insensitive K_{ATP}
401 channels (Cao et al., 2009). Since K_{ATP} channel modulators were bath applied, the
402 induced currents recorded from individual cells could also reflect network interactions
403 with neurons and/or astrocytes expressing K_{ATP} channels (Thomzig et al.,
404 2001; Matsumoto et al., 2002). However, the kinetics and reversal potential of the
405 steady state outward currents evoked by K_{ATP} channel modulations do not support an
406 indirect effect induced by transmitter release. In agreement with the observed
407 pharmacological profile (Inagaki et al., 1996) and the absence of functional K_{ATP}
408 channels in *Kcnj11*^{-/-} neurons, we observed that *Kcnj11* and *Abcc8* subunits were the
409 main components of K_{ATP} channels as detected by ribo-tag-based transcriptomics for
410 many neuronal types (Doyle et al., 2008).

411 Their low detection rate by scRT-PCR is presumably due to the low copy number of
412 their mRNAs, to the low RT efficiency and to the harvesting procedure restricted to
413 the soma. Indeed, a single-cell RNAseq study performed in mouse somatosensory
414 cortex (Zeisel et al., 2015) revealed about 5 molecules of both *Kcnj11* and *Abcc8*
415 mRNAs per cell in cortical neurons, whereas scRT-PCR detection limit was estimated
416 to be around 25 molecules of mRNA in the patch pipette (Tsuzuki et al., 2001).
417 Furthermore, since *Kcnj11* is an intronless gene, collection of the nucleus was

418 avoided to prevent potential false positives. Thus, neurons positive for both *Kcnj11*
419 and *Sst* intron, taken as an indicator of genomic DNA (Hill et al., 2007;Devienne et
420 al., 2018), were discarded from *Kcnj11* expression analysis. Unavoidably, this
421 procedure does reduce the amount of cytoplasm collected, thereby decreasing the
422 detection rate of both *Kcnj11* and *Abcc8*.

423 Consistent with the preferred expression of *Kcnj8* in mural and endothelial cells
424 (Bondjers et al., 2006;Zeisel et al., 2015;Tasic et al., 2016;Aziz et al.,
425 2017;Vanlandewijck et al., 2018;Saunders et al., 2018), this subunit was only
426 observed in one out of 277 cortical neurons analyzed. Similarly, SUR2B, the *Abcc9*
427 variant expressed in forebrain (Isomoto et al., 1996) and cortex (Figure 1-figure
428 supplement 1B), whose presence is largely restricted to vascular cells (Zeisel et al.,
429 2015), was not observed in cortical neurons.

430

431 **Relative sensitivity of cortical neurons to glucose, lactate and pyruvate**

432 Consistent with previous observations (Yang et al., 1999), decreasing extracellular
433 glucose from standard slice concentrations down to a normoglycemic level did not
434 alter firing rates of cortical neurons. However, their activity is silenced during
435 hypoglycemic episodes through K_{ATP} channels activation (Yang et al., 1999;Zawar
436 and Neumcke, 2000;Molnar et al., 2014;Sada et al., 2015). This relative glucose
437 unresponsiveness is in contrast with pancreatic beta cells and hypothalamic glucose-
438 excited neurons whose activity is regulated over a wider range of glucose
439 concentrations by K_{ATP} channels also composed with KCNJ11 and ABCC8 subunits
440 (Aguilar-Bryan et al., 1995;Inagaki et al., 1995a;Miki et al., 1998;Yang et al.,
441 1999;Miki et al., 2001;Tarasov et al., 2006;Varin et al., 2015). The inability of cortical
442 neurons to regulate their spiking activity at glucose levels beyond normoglycemia is
443 likely due to the lack of glucokinase, a hexokinase which catalyzes the first step of
444 glycolysis and acts as a glucose sensor in the millimolar range (German, 1993;Yang
445 et al., 1999). As earlier reported, hexokinase-1 (*Hk1*) is the major isoform in cortical
446 neurons (Zeisel et al., 2015;Tasic et al., 2016;Piquet et al., 2018). Since this enzyme
447 has a micromolar affinity for glucose and is inhibited by its product, glucose-6-
448 phosphate (Wilson, 2003), HK1 is likely already saturated and/or inhibited during
449 normoglycemia thereby limiting glycolysis. Nonetheless, HK1 saturation/inhibition can
450 be mitigated when energy consumption is high (Attwell and Laughlin, 2001;Wilson,
451 2003;Tantama et al., 2013), and then glucose can probably modulate neuronal

452 activity via a high affinity mechanism, as evidenced by slow oscillations of spiking
453 activity involving synaptic transmission (Cunningham et al., 2006) or by the use of
454 glucose-free whole-cell patch-clamp solution (Kawamura, Jr. et al., 2010) that mimics
455 high glucose consumption (Piquet et al., 2018;Diaz-Garcia et al., 2019).

456
457 Similarly to glucose-excited hypothalamic neurons (Yang et al., 1999;Song and
458 Routh, 2005), but in contrast with pancreatic beta cells (Newgard and McGarry,
459 1995), cortical neurons were dose-dependently excited by lactate. This lactate
460 sensitivity is consistent with lactate transport and oxidization in hypothalamic and
461 cortical neurons (Ainscow et al., 2002;Sada et al., 2015;Diaz-Garcia et al., 2017)
462 which are low in beta cells (Sekine et al., 1994;Pullen et al., 2011). Pyruvate had a
463 similar effect to lactate in cortical neurons under normoglycemic condition whereas it
464 only maintains the activity of hypothalamic glucose-excited neurons during
465 hypoglycemia (Yang et al., 1999) and barely activates pancreatic beta cells (Dufer et
466 al., 2002). Thus, cortical neurons display a peculiar metabolic sensitivity to
467 monocarboxylates. Our data also suggest that under normoglycemic conditions a
468 portion of K_{ATP} channels are open when cortical neurons fire action potentials.

469

470 **Mechanism of lactate-sensing**

471 Our pharmacological, molecular and genetic evidence indicates that the closure of
472 K_{ATP} channels is responsible for the firing rate enhancement by lactate. Since K_{ATP}
473 channels can be modulated by G protein-coupled receptors (Kawamura, Jr. et al.,
474 2010), lactate-sensing might have been mediated by GPR81, a G_i protein-coupled
475 lactate receptor expressed in the cerebral cortex (Lauritzen et al., 2014). This
476 possibility is however unlikely since the activation of GPR81 inhibits cultured cortical
477 neurons (Bozzo et al., 2013;de Castro Abrantes H. et al., 2019) and we show here
478 that enhancing effect pyruvate on neuronal activity was similar to that of lactate,
479 although pyruvate does not activate GPR81 (Ahmed et al., 2010).

480 We found that lactate-sensing was critically dependent on lactate transport and we
481 confirmed the capacity of cortical neurons to take up and oxidize lactate (Bittar et al.,
482 1996;Laughton et al., 2000;Bouzier-Sore et al., 2003;Wyss et al., 2011;Choi et al.,
483 2012;Sada et al., 2015;Machler et al., 2016). Although *Slc16a1* and *Slc16a7* mRNAs
484 were infrequently detected by scRT-PCR, our imaging and electrophysiological
485 observations indicate a widespread transport of lactate. Similarly to K_{ATP} channel

486 subunits, the relatively low single cell detection rates are likely due to the low copy
487 number of both *Slc16a1* and *Slc16a7* mRNAs which have been reported to be less
488 than 10 copies per cell in cortical neurons (Zeisel et al., 2015). Interestingly,
489 discrepancies between mRNA and protein expression have been reported for MCTs
490 (Pierre and Pellerin, 2005) which may reflect regulation at the translational level
491 and/or a low turnover of the proteins. The ability of cortical neurons to oxidize lactate
492 is supported by both scRT-PCR and NADH imaging observations. The much higher
493 detection rates of *Ldha* and *Ldhb* mRNA parallel their single cell copy number which
494 is two to five times higher than that of *Ldha* and *Ldhb* (Zeisel et al., 2015).

495 The impairment of lactate-enhanced firing by 4-CIN might be due to the blockade of
496 lactate uptake by neurons but also to the blockade of lactate efflux by astrocytes.
497 However, it is unlikely that astrocytes have a substantial contribution here. First,
498 basal lactate tone in cortical slices has been estimated to be about 200 μ M
499 (Karagiannis et al., 2015), a concentration with little or no effect on lactate-sensing
500 (Figure 5C). Second, in addition to MCTs, astrocytes can also release lactate from
501 connexin hemichannels (Karagiannis et al., 2015) and from a lactate-permeable ion
502 channel (Sotelo-Hitschfeld et al., 2015). Hence, blockade of MCTs by 4-CIN would
503 have, at most, only partially altered the release of lactate by astrocytes.

504 LDH metabolites, including pyruvate and oxaloacetate, can lead to K_{ATP} channel
505 closure (Dhar-Chowdhury et al., 2005; Sada et al., 2015) and could mediate lactate-
506 sensing. An intermediate role of oxaloacetate in lactate-sensing is compatible with
507 enhanced Krebs cycle and oxidative phosphorylation, which leads to an increased
508 ATP/ADP ratio and the closure of K_{ATP} channels (Figure 7). In contrast to
509 oxaloacetate, intracellular ATP was found to be ineffective for reverting K_{ATP} channel
510 opening induced by LDH inhibition (Sada et al., 2015). Interestingly, hippocampal
511 interneurons were found to be insensitive to glucose deprivation in whole cell
512 configuration (Sada et al., 2015) but not in perforated patch configuration (Zawar and
513 Neumcke, 2000) whereas almost the opposite was found in CA1 pyramidal cells.
514 Whether altered intracellular metabolism by whole-cell recording accounted for the
515 apparent lack of ATP sensitivity remains to be determined.

516 Increased firing rate by lactate metabolism is likely to enhance sodium influx and
517 stimulate ATP consumption by the Na^+/K^+ ATPase (Tanner et al., 2011). This could
518 in turn lower ATP/ADP ratio, increase the P_0 of K_{ATP} channels (Tantama et al., 2013)
519 and subsequently decrease firing rate. We did not observe such a decrease and,

520 once firing rate was enhanced, it remained stable for several minutes (Figure 5A).
521 This suggests that ATP levels remained relatively stable, as reported in pancreatic
522 cells under high glucose stimulation that recruits calcium dependent energy
523 metabolism (Tanaka et al., 2014). However, when energy consumption is high, as
524 during network synaptic transmission, fluctuations of ATP/ADP ratio and slow
525 oscillations of spiking activity can occur as observed in the entorhinal cortex
526 (Cunningham et al., 2006).

527

528 **Lactate as an energy substrate for neurons and an enhancer of spiking activity** 529 **and neuronal plasticity**

530 We confirmed that the ATP produced by cortical neurons was mostly derived from
531 oxidative phosphorylation and marginally from glycolysis (Almeida et al., 2001; Hall et
532 al., 2012). Together with the enhancement of spiking activity through K_{ATP} channels
533 by lactate, but not by glucose, our data support both the notion that lactate is a
534 preferred energy substrate over glucose for neonatal and juvenile cortical neurons
535 (Bouzier-Sore et al., 2003; Ivanov et al., 2011) as well as the astrocyte-neuron lactate
536 shuttle hypothesis (Pellerin and Magistretti, 1994). Whether lactate-sensing persists
537 in the adult remains to be determined.

538 Although the local cellular origin of lactate has been recently questioned (Lee et al.,
539 2012; Diaz-Garcia et al., 2017), a growing number of evidence indicates that
540 astrocytes are major central lactate producers (Almeida et al., 2001; Choi et al.,
541 2012; Sotelo-Hitschfeld et al., 2015; Karagiannis et al., 2015; Le Douce J. et al.,
542 2020; Jimenez-Blasco et al., 2020).

543 Glutamatergic synaptic transmission stimulates blood glucose uptake, astrocyte
544 glycolysis, as well as lactate release (Pellerin and Magistretti, 1994; Voutsinos-Porche
545 et al., 2003; Ruminot et al., 2011; Choi et al., 2012; Sotelo-Hitschfeld et al.,
546 2015; Lerchundi et al., 2015) and diffusion through the astroglial gap junctional
547 network (Rouach et al., 2008). This indicates that local and fast glutamatergic
548 synaptic activity would be translated by astrocyte metabolism into a widespread and
549 long-lasting extracellular lactate increase (Prichard et al., 1991; Hu and Wilson,
550 1997a), which could in turn enhance the firing of both excitatory and inhibitory
551 neurons (Figure 7). Such a lactate surge would be spatially confined by the gap
552 junctional connectivity of the astroglial network, which in layer IV represents an
553 entire barrel (Houades et al., 2008).

554 This suggests that increased astrocytic lactate induced by whisker stimulation could
555 enhance the activity of the cortical network and fine-tune upcoming sensory
556 processing for several minutes, thereby favoring neuronal plasticity. Along this line,
557 lactate derived from astrocyte glycogen supports both neuronal activity and long-term
558 memory formation (Suzuki et al., 2011;Choi et al., 2012;Vezzoli et al., 2020).
559 Similarly, cannabinoids, which notably alter neuronal processing and memory
560 formation (Stella et al., 1997), hamper lactate production by astrocytes (Jimenez-
561 Blasco et al., 2020).

562 In contrast to glucose levels, lactate levels are higher in extracellular fluid than in
563 plasma and can be as high as 5 mM under basal resting condition (Abi-Saab et al.,
564 2002;Zilberter et al., 2010). Given that extracellular lactate is almost doubled during
565 neuronal activity (Prichard et al., 1991;Hu and Wilson, 1997a), enhancement of
566 neuronal activity by lactate is likely to occur when the brain is active. Peripheral
567 lactate released by skeletal muscles, which can reach 15 mM in plasma following an
568 intense physical exercise (Quistorff et al., 2008), could also facilitate this effect.
569 Although systemic increase of lactate elevates its cerebral extracellular concentration
570 (Machler et al., 2016;Carrard et al., 2018) to a level with little or no effect on firing
571 rate, when both the brain and the body are active, as during physical exercise, both
572 astrocytes and systemic lactate could contribute to enhance spiking activity.

573 Blood-borne lactate has been shown to promote learning and memory formation via
574 brain-derived neurotrophic factor (El Hayek L. et al., 2019). It is worth noting that the
575 production of this neurotrophin is altered in *Kcnj11*^{-/-} mice and impaired by a K_{ATP}
576 channel opener (Fan et al., 2016), both conditions compromising the effect of lactate
577 on spiking activity. Hence, the increase in astrocyte and systemic lactate could fine-
578 tune neuronal processing and plasticity in a context-dependent manner and their
579 coincidence could be potentially synergistic.

580

581 **Lactate-sensing compensatory mechanisms**

582 Since excitatory neuronal activity increases extracellular lactate (Prichard et al.,
583 1991;Hu and Wilson, 1997a) and lactate enhances neuronal activity, such a positive
584 feedback loop (Figure 7) suggests that compensatory mechanisms might be
585 recruited to prevent an overexcitation of neuronal activity by lactate supply. A
586 metabolic negative feedback mechanism could involve the impairment of astrocyte

587 metabolism and lactate release by endocannabinoids (Jimenez-Blasco et al., 2020)
588 produced during intense neuronal activity (Stella et al., 1997).
589 Another possibility would consist in a blood flow decrease that would in turn reduce
590 the delivery of blood glucose and subsequent local lactate production and release but
591 also blood-borne lactate. Some GABAergic interneuron subtypes (Cauli et al.,
592 2004;Uhlirva et al., 2016;Krawchuk et al., 2019), but also astrocytes (Girouard et al.,
593 2010), can trigger vasoconstriction and blood flow decrease when their activity is
594 increased. This could provide a negative hemodynamic feedback restricting spatially
595 and temporally the increase of spiking activity by lactate.
596 PVALB-expressing and SST-expressing interneurons exhibit higher mitochondrial
597 content and apparent oxidative phosphorylation than pyramidal cells (Gulyas et al.,
598 2006) suggesting that interneurons would more rapidly metabolize and sense lactate
599 than pyramidal cells. These inhibitory GABAergic interneurons might therefore
600 silence the cortical network, thereby providing a negative neuronal feedback loop.
601 Active decrease in blood flow is associated with a decrease in neuronal activity
602 (Shmuel et al., 2002;Shmuel et al., 2006;Devor et al., 2007). Vasoconstrictive
603 GABAergic interneurons may underlie for both processes and could contribute to
604 returning the system to a low lactate state.

605

606 **Conclusion**

607 Our data indicate that lactate is both an energy substrate for cortical neurons and a
608 signaling molecule enhancing their spiking activity. This suggests that a coordinated
609 neurovascular and neurometabolic coupling would define a time window of an up
610 state of lactate that, besides providing energy and maintenance to the cortical
611 network, would fine-tune neuronal processing and favor, for example, memory
612 formation (Suzuki et al., 2011;Kann et al., 2014;Galow et al., 2014;Jimenez-Blasco et
613 al., 2020).

614

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622

623 **Competing interests**

624 The authors declare no competing interests.

625

626 **Materials and methods**

627 **Lead contact and materials availability**

628 Further information and requests for resources and reagents should be directed to,
629 and will be fulfilled by, the lead contact, B. Cauli (bruno.cauli@upmc.fr).

630

631 **Experimental model and subject details**

632 Wistar rats, C57BL/6RJ or *Kcnj11*^{-/-} (B6.129P2-*Kcnj11*^{tm1Sse}, backcrossed into
633 C57BL6 over six generations) mice were used for all experiments in accordance with
634 French regulations (Code Rural R214/87 to R214/130) and conformed to the ethical
635 guidelines of both the directive 2010/63/EU of the European Parliament and of the
636 Council and the French National Charter on the ethics of animal experimentation. A
637 maximum of 3 rats or 5 mice were housed per cage and single animal housing was
638 avoided. Male rats and mice of both genders were housed on a 12-hour light/dark
639 cycle in a temperature-controlled (21–25°C) room and were given food and water *ad*
640 *libitum*. Animals were used for experimentation at 13-24 days of age.

641

642 **Cortical slice preparation**

643 Rats or mice were deeply anesthetized with isoflurane. After decapitation brains were
644 quickly removed and placed into cold (~4°C) oxygenated artificial cerebrospinal fluid
645 (aCSF) containing (in mM): 126 NaCl, 2.5 KCl, 1.25 NaH₂PO₄, 2 CaCl₂, 1 MgCl₂, 26
646 NaHCO₃, 10 glucose, 15 sucrose, and 1 kynurenic acid. Coronal slices (300 μm
647 thick) containing the barrel cortex were cut with a vibratome (VT1000S, Leica) and
648 allowed to recover at room temperature for at least 1h in aCSF saturated with O₂/CO₂
649 (95 %/5 %) as previously described (Karagiannis et al., 2009;Devienne et al., 2018).

650

651 **Whole-cell patch-clamp recording**

652 Patch pipettes (4-6 MΩ) pulled from borosilicate glass were filled with 8 μl of RNase
653 free internal solution containing in (mM): 144 K-gluconate, 3 MgCl₂, 0.5 EGTA, 10

654 HEPES, pH 7.2 (285/295 mOsm). Whole-cell recordings were performed at $25.3 \pm$
655 0.2°C using a patch-clamp amplifier (Axopatch 200B, Molecular Devices). Data were
656 filtered at 5-10 kHz and digitized at 50 kHz using an acquisition board (Digidata 1440,
657 Molecular Devices) attached to a personal computer running pCLAMP 10.2 software
658 package (Molecular Devices). For ATP washout experiments neurons were recorded
659 in voltage clamp mode using an ATP-free internal solution containing in (mM): 140
660 KCl, 20 NaCl, 2 MgCl_2 , 10 EGTA, 10 HEPES, pH 7.2.

661

662 **Cytoplasm harvesting and scRT-PCR**

663 At the end of the whole-cell recording, lasting less than 15 min, the cytoplasmic
664 content was aspirated in the recording pipette. The pipette's content was expelled
665 into a test tube and reverse transcription (RT) was performed in a final volume of 10
666 μl , as described previously (Lambolez et al., 1992). The scRT-PCR protocol was
667 designed to probe simultaneously the expression of neuronal markers, K_{ATP} channels
668 subunits or some key elements of lactate metabolism. Two-steps amplification was
669 performed essentially as described (Cauli et al., 1997; Devienne et al., 2018). Briefly,
670 cDNAs present in the 10 μl reverse transcription reaction were first amplified
671 simultaneously using all external primer pairs listed in the Key Ressources Table.
672 Taq polymerase and 20 pmol of each primer were added to the buffer supplied by the
673 manufacturer (final volume, 100 μl), and 20 cycles (94°C , 30 s; 60°C , 30 s; 72°C , 35
674 s) of PCR were run. Second rounds of PCR were performed using 1 μl of the first
675 PCR product as a template. In this second round, each cDNA was amplified
676 individually using its specific nested primer pair (Key Ressources Table in Appendix)
677 by performing 35 PCR cycles (as described above). 10 μl of each individual PCR
678 product were run on a 2 % agarose gel stained with ethidium bromide using ΦX174
679 digested by *HaeIII* as a molecular weight marker.

680

681 **Perforated patch-clamp recording**

682 Gramicidin stock solution (2 mg/ml, Sigma-Aldrich) was prepared in DMSO and
683 diluted to 10-20 $\mu\text{g/ml}$ (Zawar and Neumcke, 2000) in the RNase free internal
684 solution described above. The pipette tip was filled with gramicidin-free solution.
685 Progress in perforation was evaluated by monitoring the capacitive transient currents
686 elicited by -10 mV voltage pulses from a holding potential of -60 mV. In perforated
687 patch configuration, a continuous current (52 ± 7 pA) was injected to induce the

688 spiking of action potentials at stable firing rates of 4.1 ± 0.4 Hz obtained after an
689 equilibration period of 3.6 ± 0.5 min. Membrane and access resistance were
690 continuously monitored by applying -50 pA hyperpolarizing current pulses lasting 1 s
691 every 10 s using an external stimulator (S900, Dagan) connected to the amplifier.
692 Recordings were stopped when going into whole-cell configuration occurred, as
693 evidenced by sudden increase of spike amplitude and decrease of access
694 resistance.

695

696 **NADH imaging**

697 Recordings were made in layer II-III of the rat somatosensory cortex. Wide-field
698 fluorescent images were obtained using a double port upright microscope BX51WI,
699 WI-DPMC, Olympus) with a 60x objective (LUMPlan FI /IR 60x/0.90 W, Olympus)
700 and a digital camera (CoolSnap HQ2, Roper Scientific) attached on the front port of
701 the microscope. NADH autofluorescence was obtained by 365 nm excitation with a
702 Light Emitting Device (LED, pE-2, CoolLED) using Imaging Workbench 6.0.25
703 software (INDEC Systems) and dichroic (FF395/495/610-Di01-25x36, Semrock) and
704 emission filters (FF01-425/527/685-25, Semrock). Infrared Dodt gradient contrast
705 images (IR-DGC, (Dodt and Zieglgansberger, 1998)) were obtained using a 780 nm
706 collimated LED (M780L3-C1, Thorlabs) as a transmitted light source and DGC optics
707 (Luigs and Neumann). Autofluorescence and IR-DGC images were collected every
708 10s by alternating the fluorescence and transmitted light sources. In parallel, infrared
709 transmitted light images of slices were also continuously monitored on the back-port
710 of the microscope using a customized beam splitter (725 DCSPXR, Semrock) and an
711 analogic CCD camera (XC ST-70 CE, Sony). The focal plane was maintained
712 constant on-line using infrared DGC images of cells as anatomical landmarks
713 (Lacroix et al., 2015).

714

715 **Subcloning and viral production**

716 The coding sequence of the ATP sensor ATeam1.03YEMK (Imamura et al., 2009)
717 was subcloned into the viral vector pSinRep5. Sindbis virus was produced as
718 previously described (Piquet et al., 2018). Recombinant pSinRep5 and helper
719 plasmid pDH26S (Invitrogen) were transcribed in vitro into capped RNA using the
720 Megascript SP6 kit (Ambion). Baby hamster kidney-21 cells (BHK-21, clone 13,
721 *Mesocricetus auratus*, hamster, Syrian golden), negative for mycoplasma

722 contamination and purchased from ATCC (CCL-10, RRID:CVCL_1915, lot number
723 1545545), were only used for viral production. BHK-21 cells were electroporated with
724 sensor-containing RNA and helper RNA ($2 \cdot 10^7$ cells, 950 μ F, 230 V) and incubated
725 for 24 h at 37°C in 5% CO₂ in Dulbecco's modified Eagle Medium supplemented with
726 5% fetal calf serum before collecting cell supernatant containing the viruses. The
727 virus titer (10^8 infectious particles/ml) was determined after counting fluorescent baby
728 hamster kidney cells infected using serial dilution of the stock virus.

729

730 **Brain slice viral transduction**

731 Brain slices were placed onto a millicell membrane (Millipore) with culture medium
732 (50% minimum essential medium, 50% Hank's balanced salt sodium, 6.5 g/l glucose
733 and 100 U/ml penicillin-streptomycin (Sigma-Aldrich) as previously described (Piquet
734 et al., 2018). Infection was performed by adding $\sim 5 \times 10^5$ particles per slice. Slices
735 were incubated overnight at 35°C in 5% CO₂. The next morning, brain slices were
736 equilibrated for 1h in aCSF containing (in mM): 126 NaCl, 2.5 KCl, 1.25 NaH₂PO₄, 2
737 CaCl₂, 1 MgCl₂, 26 NaHCO₃, 10 glucose, 15 sucrose. Slices were then placed into
738 the recording chamber, heated at ~ 30 °C and continuously perfused at 1-2 ml/min.

739

740 **FRET imaging**

741 Recordings were made from visually identified pyramidal cells in layer II-III of the rat
742 somatosensory cortex. Wide-field fluorescent images were obtained using a 40x
743 objective and a digital camera attached on the front port of the microscope. The ATP
744 sensor ATeam1.03YEMK was excited at 400 nm with a LED using Imaging
745 Workbench 6.0.25 software and excitation (FF02-438/24-25, Semrock) and dichroic
746 filters (FF458-Di02-25x36, Semrock). Double fluorescence images were collected
747 every 15s by alternating the fluorescence emission filters for the CFP (FF01-483/32-
748 25, Semrock) and the YFP (FF01-542/27-25, Semrock) using a filter wheel (Lambda
749 10B, Sutter Instruments). The focal plane was maintained constant on-line as
750 described above.

751

752 **Pharmacological studies**

753 Pinacidil (100 μ M, Sigma-Aldrich); Diazoxide (300 μ M, Sigma-Aldrich) and
754 Tolbutamide (500 μ M, Sigma-Aldrich), Mn(III)tetrakis(1-methyl-4-pyridyl)porphyrin
755 (MnTMPyP, 25 μ M, Millipore), α -cyano-4-hydroxycinnamate (4-CIN, 250 μ M, Sigma-

756 Aldrich); iodoacetic acid (IAA, 200 μ M, Sigma-Aldrich) or KCN (1 mM, Sigma-Aldrich)
757 was dissolved in aCSF from stock solutions of pinacidil (100 mM; NaOH 1M),
758 diazoxide (300 mM; NaOH 1M), tolbutamide (500 mM; NaOH 1M), 4-CIN (250 mM;
759 DMSO), IAA (200 mM, water) and KCN (1 M, water). Changes in extracellular
760 glucose, lactate or pyruvate concentration were compensated by changes in sucrose
761 concentration to maintain the osmolarity of the aCSF constant as previously
762 described (Miki et al., 2001;Varin et al., 2015;Piquet et al., 2018) and pH was
763 adjusted to 7.4.

764

765 **Quantification and statistical analysis**

766 **Analysis of somatic features**

767 The laminar location determined by infrared videomicroscopy and recorded as 1-4
768 according to a location right within layers I, II/III or IV. For neurons located at the
769 border of layers I-II/III and II/III-IV, the laminar location was represented by 1.5 and
770 3.5, respectively. Somatic features were measured from IR DGC of the recorded
771 neurons. Briefly, the soma was manually delineated using Image-Pro Analyzer 7.0
772 software (MediaCybernetics) and length of major and minor axes, perimeter and area
773 were extracted. The soma elongation was calculated as the ratio between major and

774 minor axis. Roundness was calculated according to: $\frac{perimeter^2}{4\pi \times area}$; a value close to 1 is
775 indicative of round somata.

776

777 **Analysis of electrophysiological properties**

778 32 electrophysiological properties chosen to describe the electrophysiological
779 diversity of cortical neurons (Ascoli et al., 2008) were determined using the I-clamp
780 fast mode of the amplifier as previously described (Karagiannis et al., 2009).
781 Membrane potential values were corrected for theoretical liquid junction potential (-
782 15.6 mV). Resting membrane potential was measured just after passing in whole-cell
783 configuration, and only cells with a resting membrane potential more negative than -
784 55 mV were analyzed further. Membrane resistance (R_m) and membrane time
785 constant (τ_m) were determined on responses to hyperpolarizing current pulses
786 (duration, 800 ms) eliciting voltage shifts of 10-15 mV negative to rest (Kawaguchi,
787 1993;Kawaguchi, 1995). Time constant was determined by fitting this voltage

788 response to a single exponential. Membrane capacitance (C_m) was calculated
789 according to $C_m = \tau_m / R_m$. Sag index was quantified as a relative decrease in
790 membrane conductance according to $(G_{sag} - G_{hyp}) / G_{sag}$ (Halabisky et al., 2006) where
791 G_{hyp} and G_{sag} correspond to the whole-cell conductance when the sag was inactive
792 and active, respectively. G_{sag} was measured as the slope of the linear portion of a
793 current–voltage (I–V) plot, where V was determined at the end of 800 ms
794 hyperpolarizing current pulses (-100 to 0 pA) and G_{hyp} as the slope of the linear
795 portion of an I–V plot, where V was determined as the maximal negative potential
796 during the 800 ms hyperpolarizing pulses. Rheobase was quantified as the minimal
797 depolarizing current pulse intensity (800 ms duration pulses, 10 pA increments)
798 generating at least one action potential. First spike latency (Gupta et al., 2000; Ascoli
799 et al., 2008) was measured at rheobase as the time needed to elicit the first action
800 potential. To describe different firing behaviors near threshold, spike frequency was
801 measured near spike threshold on the first trace in which at least three spikes were
802 triggered. Instantaneous discharge frequencies were measured and fitted to a
803 straight line according to $F_{threshold} = m_{threshold} \cdot t + F_{min.}$, where $m_{threshold}$ is the slope
804 termed adaptation, t the time and $F_{min.}$ the minimal steady state frequency. Analysis
805 of the action potentials waveforms was done on the first two spikes. Their amplitude
806 (A1 and A2) was measured from threshold to the positive peak of the spike. Their
807 duration (D1 and D2) was measured at half amplitude (Kawaguchi, 1993; Cauli et al.,
808 1997). Their amplitude reduction and the duration increase were calculated
809 according to $(A1 - A2) / A1$ and $(D2 - D1) / D1$, respectively (Cauli et al., 1997; Cauli et al.,
810 2000). The amplitude and the latency of the fast and medium afterhyperpolarization
811 (fAH and mAH) were measured for the first two action potentials as the difference
812 between spike threshold and the negative peak of the AHs (Kawaguchi, 1993). The
813 amplitude and latency of afterdepolarization (AD) following single spikes (Haj-
814 Dahmane and Andrade, 1997) were measured as the difference between the
815 negative peak of the fAH and the peak of the AD and between the spike threshold
816 and the peak of the AD, respectively. When neurons did not exhibit mAH or AD,
817 amplitude and latency were arbitrarily set to 0. A complex spike amplitude
818 accommodation during a train of action potentials, consisting in a transient decrease
819 of spikes amplitude, was measured as the difference between the peak of the
820 smallest action potential and the peak of the following largest action potential (Cauli
821 et al., 2000). Maximal firing rate was defined as the last trace before prominent

822 reduction of action potentials amplitude indicative of a saturated discharge. To take
823 into account the biphasic spike frequency adaptation (early and late) occurring at
824 high firing rates (Cauli et al., 1997;Cauli et al., 2000;Gallopín et al., 2006),
825 instantaneous firing frequency was fitted to a single exponential (Halabisky et al.,
826 2006) with a sloping baseline, according to : $F_{Saturation} = A_{sat} \cdot e^{-t/\tau_{sat}} + t \cdot m_{sat} + F_{max}$, where
827 A_{sat} corresponds to the amplitude of early frequency adaptation, τ_{sat} to the time
828 constant of early adaptation, m_{sat} to the slope of late adaptation and F_{max} to the
829 maximal steady state frequency.

830

831 **Unsupervised clustering**

832 To classify neurons unsupervised clustering was performed using the laminar
833 location of the soma, 10 molecular parameters (*Slc17a7*, *Gad2* and/or *Gad1*, *Nos1*,
834 *Calb1*, *Pvalb*, *Calb2*, *Npy*, *Vip*, *Sst* and *Cck*) and the 32 electrophysiological
835 parameters described above. Neurons positive for *Gad2* and/or *Gad1* were denoted
836 as *Gad* positive and these mRNAs were considered as a single molecular variable as
837 previously described (Gallopín et al., 2006). Parameters were standardized by
838 centering and reducing all of the values. Cluster analysis was run on Statistica 6.1
839 software (Statsoft) using Ward's method (Ward, 1963). The final number of clusters
840 was established by hierarchically subdividing the clustering tree into higher order
841 clusters as previously described (Karagiannis et al., 2009).

842

843 **Analysis of voltage clamp recordings**

844 Whole-cell currents were measured from a holding potential of -70 mV and
845 membrane resistances were determined by applying a voltage step to -60 mV of 100
846 ms every 5 s. The effects of K_{ATP} channel modulators were measured at the end of
847 drug application by averaging, over a period of 1 minute, whole cell currents and
848 changes in membrane resistance relative to control baseline prior to the application
849 of drugs. Whole-cell K_{ATP} current and conductance were determined by subtracting
850 current and conductance measured under K_{ATP} channel activator by their value
851 measured under K_{ATP} channel blocker. The relative whole-cell K_{ATP} conductance was
852 determined by dividing the whole-cell K_{ATP} conductance by the whole cell
853 conductance measured under K_{ATP} channel activator. Whole-cell K_{ATP} current density

854 was determined by dividing the whole-cell K_{ATP} current by the membrane
855 capacitance. K_{ATP} current reversal potential was measured by subtracting I/V
856 relationships obtained during voltage ramps from -60 to -130 mV determined under
857 K_{ATP} channel activator and blocker, respectively.

858 During ATP washout experiments, whole-cell currents and I/V relationships were
859 measured every 10 s at a holding potential of -50 mV and during voltage ramps from
860 -40 to -120 mV, respectively. Washout currents were determined by subtracting the
861 whole-cell currents measured at the beginning and the end of the whole cell-
862 recording, respectively.

863

864 **Analysis of current clamp recordings**

865 Every 10 s, membrane potential and mean firing rate were measured and membrane
866 resistances were determined from voltage responses induced by -50 pA currents
867 pulses lasting 1 s. K_{ATP} voltage response and changes in membrane resistance and
868 firing rate were determined by subtracting their value measured under K_{ATP} channel
869 activator by their value measured under K_{ATP} channel blocker. Neurons were
870 considered as responsive to K_{ATP} channel modulators if the K_{ATP} channel activator
871 induced both a hyperpolarization and a decrease in membrane resistance reversed
872 by the K_{ATP} channel blocker.

873

874 **Analysis of perforated patch recordings**

875 Mean firing frequency was measured every 10 s. Quantification of spiking activity
876 was determined by averaging firing frequency over a period of 5 min preceding a
877 change in extracellular aCSF composition. Firing frequencies were normalized by the
878 averaged mean firing frequency measured under control condition.

879

880 **NADH imaging**

881 Shading correction was applied off-line on the NADH autofluorescence images using
882 the "Shading Corrector" plugin of FIJI software (Schindelin et al., 2012) and a blank
883 field reference image. To compensate for potential x-y drifts all IR-DGC images were
884 realigned off-line using the "StackReg" and "TurboReg" plugins (Thevenaz et al.,
885 1998) of FIJI software and the same registration was applied to the corrected NADH
886 autofluorescence images. To determine somatic regions of interest (ROIs) the soma
887 was manually delineated on IR-DGC images. The mean NADH autofluorescence

888 was measured at each time point using the same ROIs. Variations of fluorescence
889 intensity were expressed as the ratio $(F-F_0)/F_0$ where F corresponds to the mean
890 fluorescence intensity in the ROI at a given time point, and F_0 corresponds to the
891 mean fluorescence intensity in the same ROI during the 5 min control baseline prior
892 to changes in aCSF composition. Effect of monocarboxylate superfusion or oxidative
893 phosphorylation blockade was quantified by averaging the normalized ratio (R/R_0)
894 during the last five minutes of drug application.

895

896 **FRET imaging**

897 All images were realigned off-line as described above using the YFP images as the
898 reference for registration. Fluorescence ratios were calculated by dividing the
899 registered YFP images by the registered CFP images using FIJI. The somatic ROIs
900 were manually delineated on the YFP images as described above. The mean ratio
901 was measured at each time point using the same ROIs. Variations of fluorescence
902 ratio were expressed as the ratio $(R-R_0)/R_0$ where R corresponds to the
903 fluorescence ratio in the ROI at a given time point, and R_0 corresponds to the mean
904 fluorescence ratio in the same ROI during the 10 min control baseline prior to drug
905 application. Effect of glycolysis or oxidative phosphorylation blockade was quantified
906 by averaging the normalized ratio during the last five minutes of drug application.

907

908 **Statistical analysis**

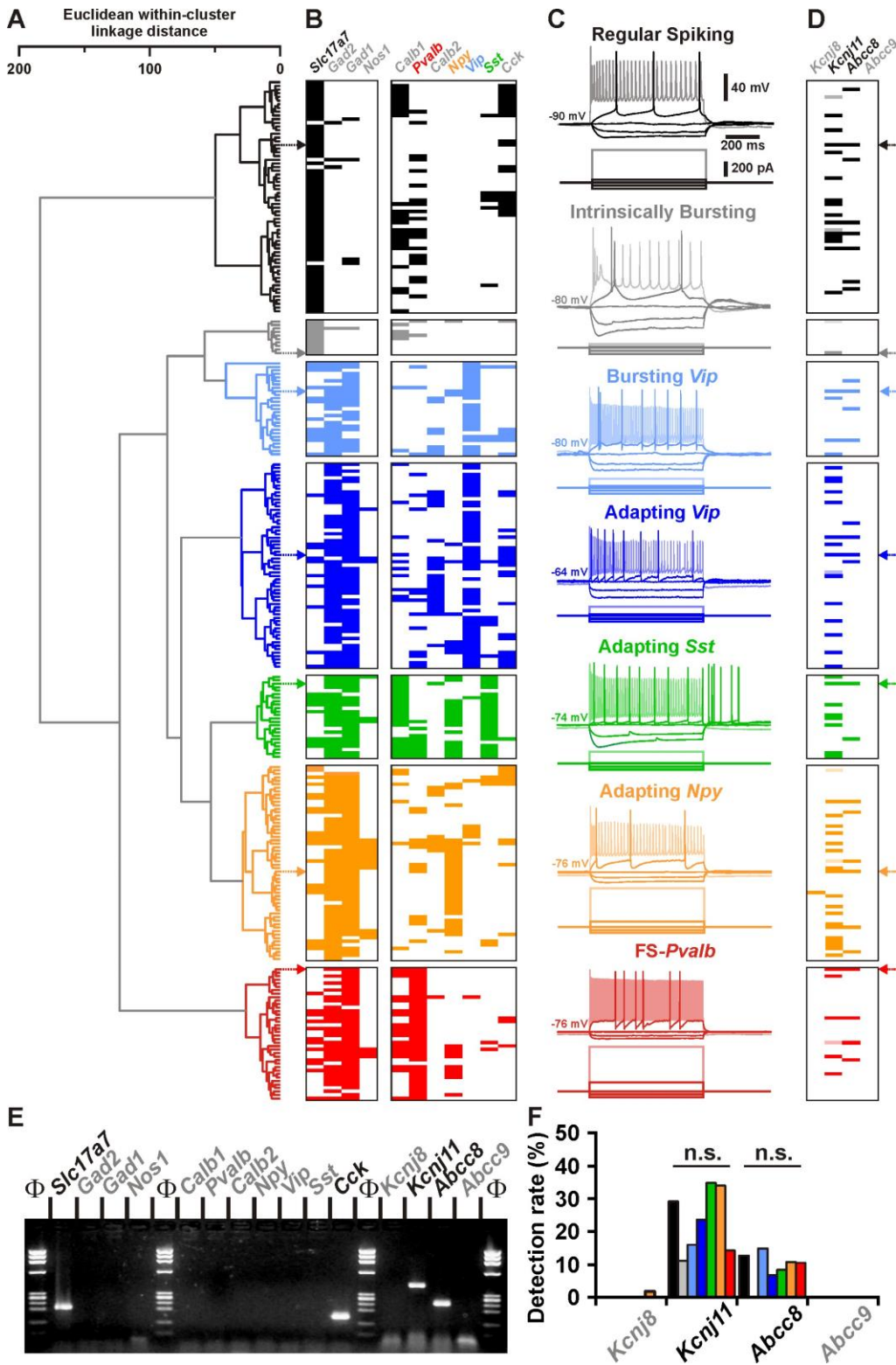
909 Statistical analyses were performed with Statistica 6.1 and GraphPad Prism 7. All
910 values are expressed as means \pm s.e.m. Normality of distributions and equality of
911 variances were assessed using the Shapiro–Wilk test and the Fisher F-test,
912 respectively. Parametric tests were only used if these criteria were met. Holm-
913 Bonferroni correction was used for multiple comparisons and p-values are given as
914 uncorrected. Statistical significance on all figures uses the following convention of
915 corrected p-values: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

916 Statistical significance of morphological and electrophysiological properties of
917 neurons was determined using the Mann-Whitney U test. Comparison of the
918 occurrence of expressed genes and of responsiveness of K_{ATP} channel modulators
919 between different cell types was determined using Fisher's exact test. Statistical
920 significance of the effects of K_{ATP} channel modulators was determined using the
921 Friedman and post hoc Dunn's tests. Significance of the effect of the ROS scavenger

922 was determined using one-tailed unpaired student t-test. Comparison of K_{ATP} channel
923 properties was determined using Mann-Whitney U, Student-t, or Kruskal-Wallis H
924 tests. Comparison of responses between *Kcnj11*^{+/+} and *Kcnj11*^{-/-} neurons was
925 determined using Mann-Whitney U test. Statistical significance of the effects of
926 energy substrates and drug applications on evoked firing in perforated patch
927 recordings was determined using Friedman and Dunn's tests. Comparison of the
928 effects of monocarboxylates and cyanide on NADH fluorescence was determined
929 using Mann-Whitney U test. Statistical significance of the effects of metabolic
930 inhibitors on intracellular ATP was determined using Friedman and Dunn's tests.
931

932 **Figure legends**

933 **Figure 1. Detection of *Kcnj11* and *Abcc8* K_{ATP} channel subunits in cortical**
 934 **neuron subtypes.**



935

936

937 (A) Ward's clustering of 277 cortical neurons (left panel). The x axis represents the
 938 average within-cluster linkage distance, and the y axis the individuals.

939 (B) Gene detection profile across the different cell clusters. For each cell, colored and
 940 white rectangles indicate presence and absence of genes, respectively. (C)
 941 Representative voltage responses induced by injection of current pulses (bottom
 942 traces) corresponding to -100, -50 and 0 pA, rheobase and intensity inducing a
 943 saturating firing frequency (shaded traces) of a Regular Spiking neuron (black), an
 944 Intrinsically Bursting neuron (gray), a Bursting *Vip* interneuron (light blue), an
 945 Adapting *Vip* interneuron (blue), an Adapting *Sst* interneuron (green), an Adapting
 946 *Npy* interneuron (orange), and a Fast Spiking-Parvalbumin interneuron (FS-*Pvalb*,
 947 red). The colored arrows indicate the expression profiles of neurons whose firing
 948 pattern is illustrated in (C).

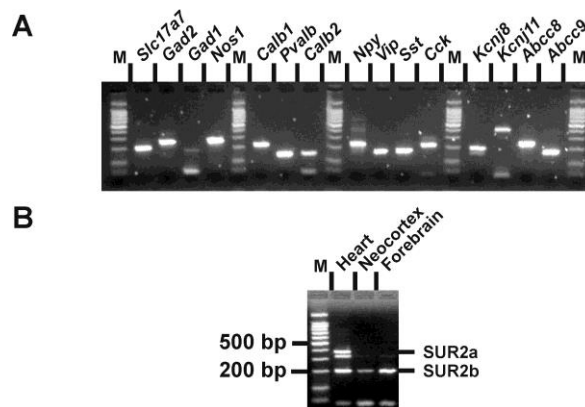
949 (D) Detection of the subunits of the K_{ATP} channels in the different clusters. Shaded
 950 rectangles represent potential *Kcnj11* false positives in which genomic DNA was
 951 detected in the harvested material.

952 (E) scRT-PCR analysis of the RS neuron depicted in (A-D).

953 (F) Histograms summarizing the detection rate of K_{ATP} channel subunits in identified
 954 neuronal types. n.s. not statistically significant.

955

956 **Figure 1-figure supplement 1. Molecular expression of K_{ATP} channels.**



957

958

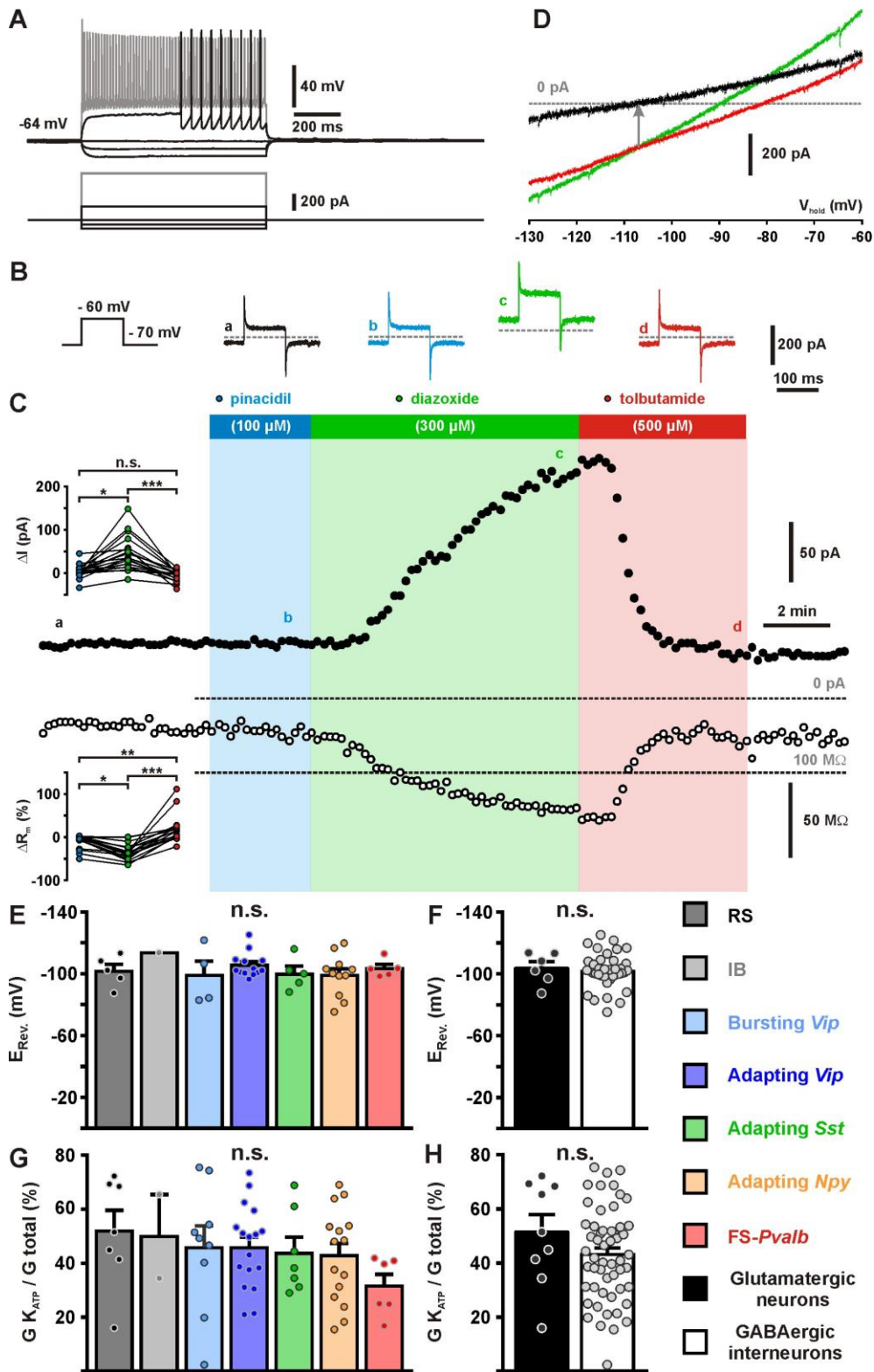
959 (A) RT-PCR products generated from 500 pg of total cortical RNAs. M: 100 bp ladder
 960 molecular weight marker.

961 (B) *Abcc9* splice variants-specific RT-PCR analysis of 1 ng total RNAs from rat heart,
 962 neocortex and forebrain.

963

964 **Figure 2. Pharmacological and biophysical characterization of K_{ATP} channels in**
 965 **cortical neurons.**

966



967

968

969 (A) Representative voltage responses of a FS-*Pvalb* interneuron induced by injection
970 of current pulses (bottom traces).

971 (B) Protocol of voltage pulses from -70 to -60 mV (left trace). Responses of whole-
972 cell currents in the FS-*Pvalb* interneurons shown in (A) in control condition (black)
973 and in presence of pinacidil (blue), piazoxide (green) and tolbutamide (red) at the
974 time indicated by a-d in (C).

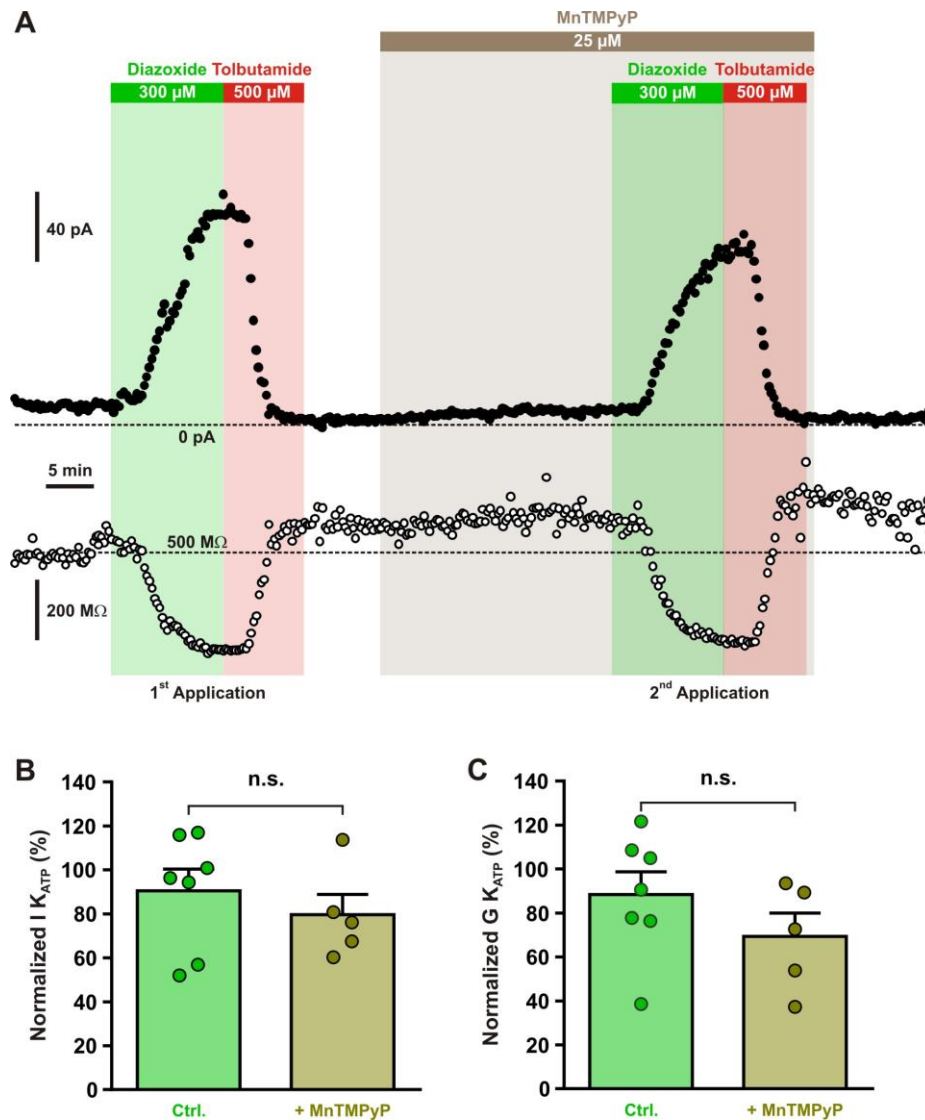
975 (C) Stationary currents recorded at -60 mV (filled circles) and membrane resistance
976 (open circles) changes induced by K_{ATP} channel modulators. The colored bars and
977 shaded zones indicate the duration of application of K_{ATP} channel modulators. Upper
978 and lower insets: changes in whole-cell currents and relative changes in membrane
979 resistance induced by K_{ATP} channel modulators, respectively.

980 (D) Whole cell current-voltage relationships measured under diazoxide (green trace)
981 and tolbutamide (red trace). K_{ATP} I/V curve (black trace) obtained by subtracting the
982 curve under diazoxide by the curve under tolbutamide. The arrow indicates the
983 reversal potential of K_{ATP} currents.

984 (E-H) Histograms summarizing the K_{ATP} current reversal potential (E,F) and relative
985 K_{ATP} conductance (G,H) in identified neuronal subtypes (E,G) or between
986 glutamatergic and GABAergic neurons (F,G). Data are expressed as mean \pm s.e.m.,
987 and the individual data points are depicted. n.s. not statistically significant.

988

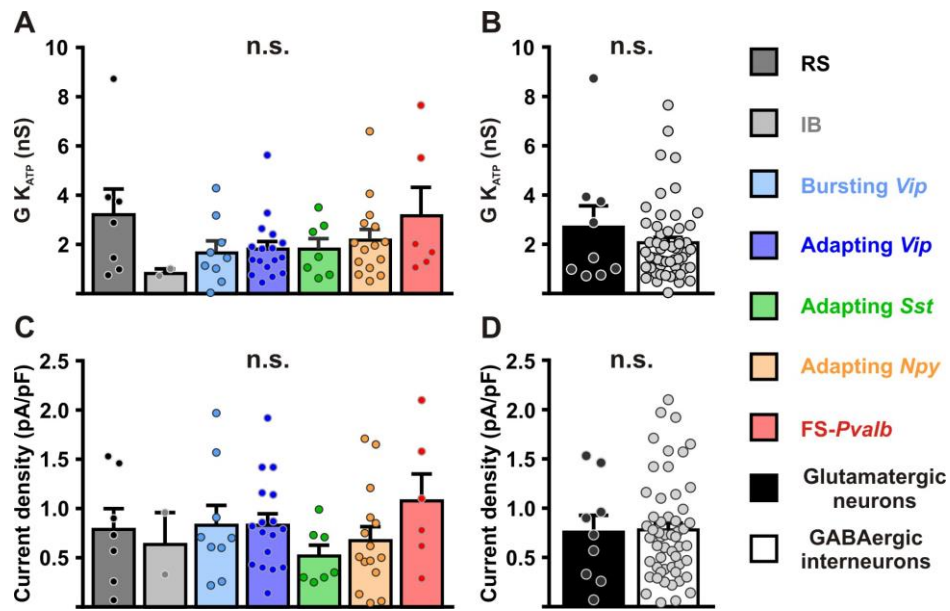
989 **Figure 2-figure supplement 1. Diazoxide-induced current is independent of**
 990 **ROS production.**



991
 992 (A) Representative stationary currents at -60 mV (filled circles) and membrane
 993 resistance (open circles) changes induced by diazoxide and tolbutamide under
 994 control condition and in presence of the superoxide dismutase and catalase mimetic,
 995 MnTMPyP. The colored bars and shaded zones indicate the duration of application.
 996 (B-C) Histograms summarizing the relative K_{ATP} currents (B) and relative whole-cell
 997 K_{ATP} conductance (C) evoked by two consecutive diazoxide and tolbutamide
 998 applications in control condition (Ctrl.) and after the presence of MnTMPyP. Data are
 999 normalized by the data measured during first application, expressed as mean ±
 1000 s.e.m., and the individual data points are depicted. n.s. not statistically significant.

1001

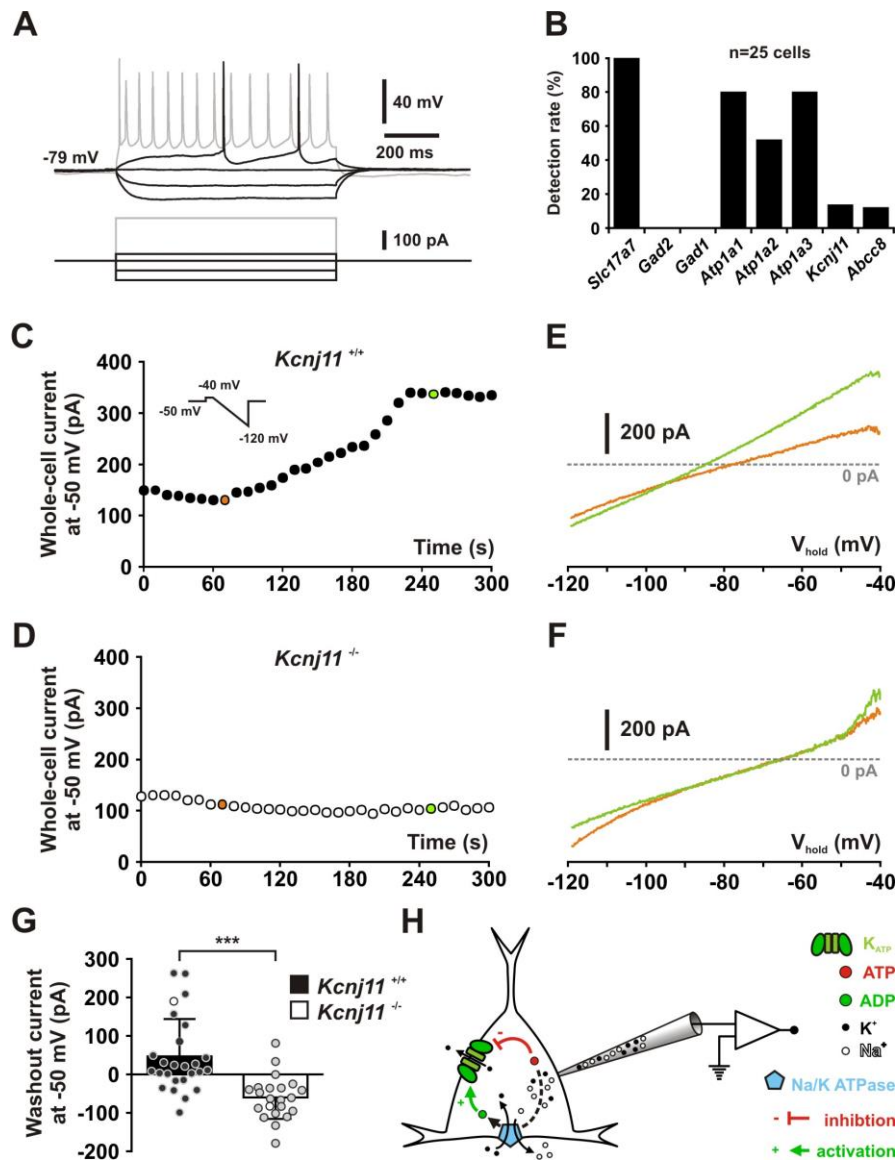
1002 **Figure 2-figure supplement 2. Characterization of K_{ATP} channels in different**
1003 **cortical neurons.**



1004
1005 (A-D) Histograms summarizing the whole-cell K_{ATP} conductance (A, B) and K_{ATP}
1006 current density (C, D) and K_{ATP} current reversal potential in identified neuronal
1007 subtypes (A,C) or between glutamatergic and GABAergic neurons (B,D). Data are
1008 expressed as mean \pm s.e.m., and the individual data points are depicted. n.s. not
1009 statistically significant.

1010

1011 **Figure 3. KCNJ11 is the pore forming subunit of K_{ATP} channels in cortical**
 1012 **neurons.**



1013
 1014
 1015 (A) Representative voltage responses of a mouse layer II/III RS pyramidal cell
 1016 induced by injection of current pulses (bottom traces).
 1017 (B) Histograms summarizing the detection rate of *Slc17a7*, *Gad2* and *1*, the *Atp1a1-3*
 1018 subunits of the Na/K ATPase and the *Kcnj11* and *Abcc8* K_{ATP} channel subunits in
 1019 layer II/III RS pyramidal cells from *Kcnj11*^{+/+} mice.
 1020 (C, D) Whole-cell stationary currents recorded at -50 mV during dialysis with ATP-
 1021 free pipette solution in cortical neurons of *Kcnj11*^{+/+} (C) and *Kcnj11*^{-/-} (D) mice. Inset;
 1022 voltage clamp protocol.

1023 (E, F) Current-voltage relationships obtained during ATP washout at the time
1024 indicated by green and orange circles in (C, D) in cortical neurons of *Kcnj11*^{+/+} (E)
1025 and *Kcnj11*^{-/-} (F) mice.

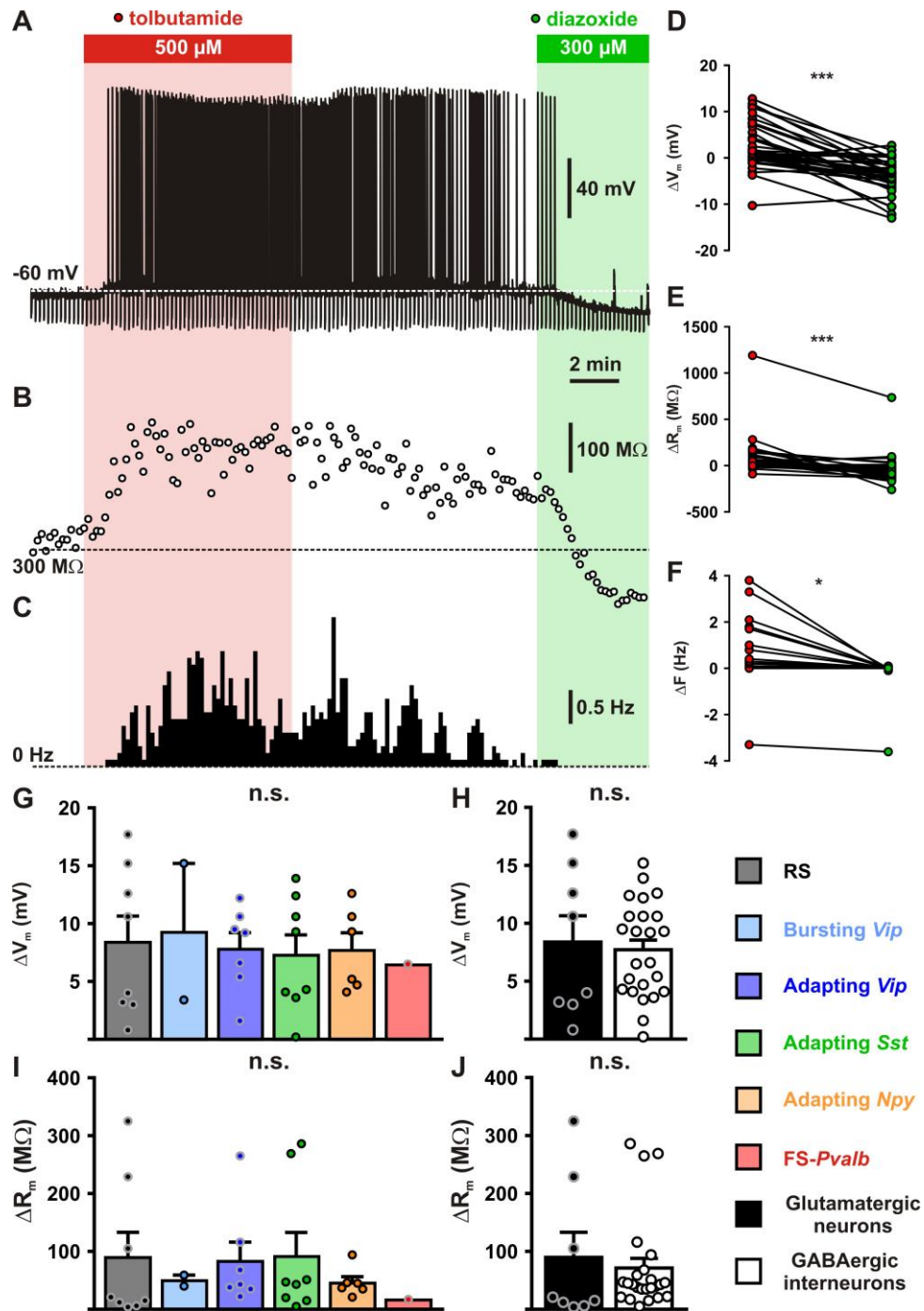
1026 (G) Histograms summarizing the whole-cell ATP washout currents in *Kcnj11*^{+/+}
1027 (black) and *Kcnj11*^{-/-} (white) cortical neurons. Data are expressed as mean ± s.e.m.,
1028 and the individual data points are depicted. Open symbols in *Kcnj11*^{+/+} and *Kcnj11*^{-/-}
1029 bar plots indicate the cells illustrated in (C,D) and (E,F), respectively.

1030 (H) Diagram depicting the principle of the ATP washout experiment.

1031

1032

1033 **Figure 4. Modulation of cortical neuronal excitability and activity by K_{ATP}**
 1034 **channels.**



1035
 1036

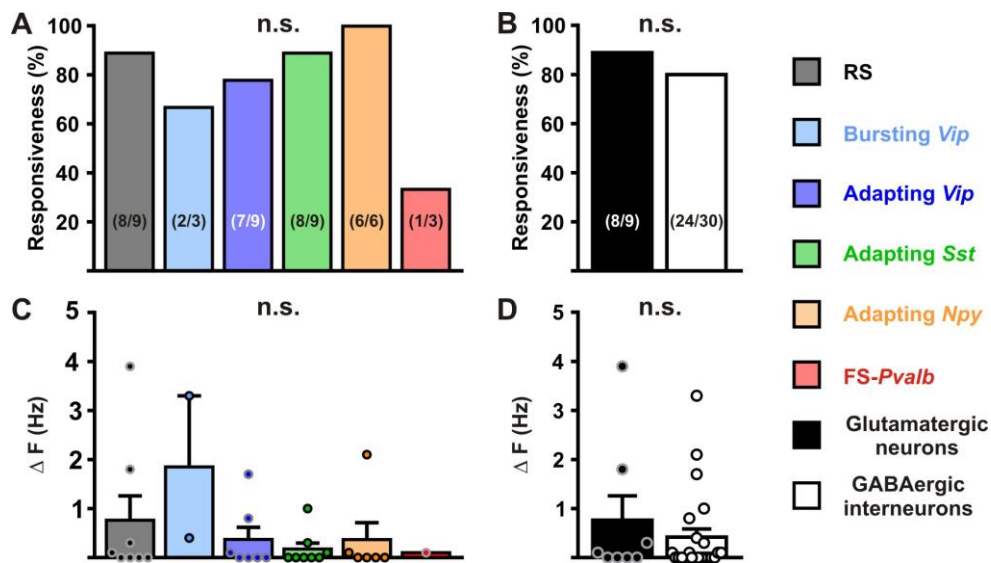
1037 (A-C) Representative example of a RS neurons showing the changes in membrane
 1038 potential (A), resistance (B, open circles) and spiking activity (C) induced by
 1039 application of tolbutamide (red) and diazoxide (green). The colored bars and shaded
 1040 zones indicate the application duration of K_{ATP} channel modulators.

1041 (D-F) Relative changes in membrane potential (D), resistance (E) and firing rate (F)
 1042 induced by tolbutamide and diazoxide in cortical neurons.

1043 (G-J) Histograms summarizing the modulation of membrane potential (G, $H_{(5,32)}=$
 1044 0.15856 , $p=0.999$, and H, $U_{(8,24)}=96$, $p=1.0000$) and resistance (I, $H_{(5,32)}=$ 2.7566 ,
 1045 $p=0.737$, and J, $U_{(8,24)}=73$, $p=0.3345$) by K_{ATP} channels in neuronal subtypes (G, I)
 1046 and groups (H, J). Data are expressed as mean \pm s.e.m., and the individual data
 1047 points are depicted. n.s. not statistically significant.

1048

1049 **Figure 4-figure supplement 1. Modulation of neuronal activity in different**
 1050 **cortical neurons by K_{ATP} channels.**



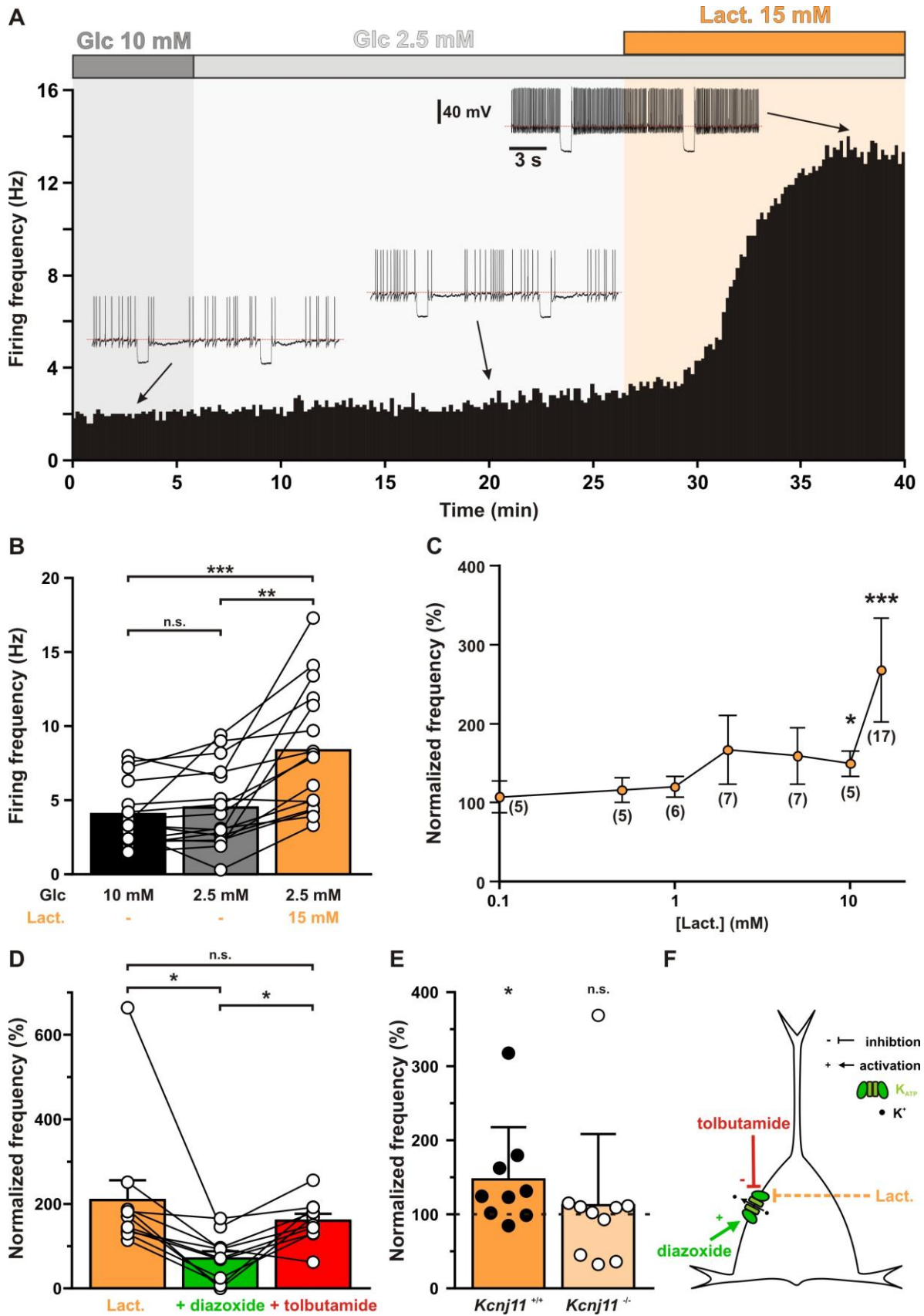
1051

1052

1053 (A-D) Histograms summarizing the proportion of responsive neurons (A,
 1054 $K^2_{(5)}=7.3125$, $p=0.1984$, and B, $p=1.0000$) and modulation firing rate (C, $H_{(5,32)}=$
 1055 5.0202 , $p=0.413$, and D, $U_{(8,24)}=87$, $p=0.7169$) by K_{ATP} channels in neuronal subtypes
 1056 (A,C) and groups (B,D). The numbers in brackets indicate the number of responsive
 1057 cells and analyzed cells, respectively. Data are expressed as mean \pm s.e.m., and the
 1058 individual data points are depicted. n.s. not statistically significant.

1059

1060 **Figure 5. Lactate enhances cortical neuronal activity via K_{ATP} channel**
 1061 **modulation.**



1062
 1063

1064 (A) Representative perforated patch recording of an adapting VIP neuron showing
1065 the modulation of firing frequency induced by changes in the extracellular
1066 concentrations of metabolites. The colored bars and shaded zones indicate the
1067 concentration in glucose (grey) and lactate (orange). Voltage responses recorded at
1068 the time indicated by arrows. The red dashed lines indicate -40 mV.

1069 (B) Histograms summarizing the mean firing frequency during changes in
1070 extracellular concentration of glucose (black and grey) and lactate (orange). Data are
1071 expressed as mean \pm s.e.m., and the individual data points are depicted. n.s. not
1072 statistically significant.

1073 (C) Dose-dependent enhancement of firing frequency by lactate. Data are normalized
1074 by the mean firing frequency in absence of lactate and are expressed as mean \pm
1075 s.e.m. Numbers in brackets indicate the number of recorded neurons at different
1076 lactate concentrations.

1077 (D) Histograms summarizing the normalized frequency under 15 mM lactate (orange)
1078 and its modulation by addition of diazoxide (green) or tolbutamide (red). Data are
1079 expressed as mean \pm s.e.m., and the individual data points are depicted. n.s. not
1080 statistically significant.

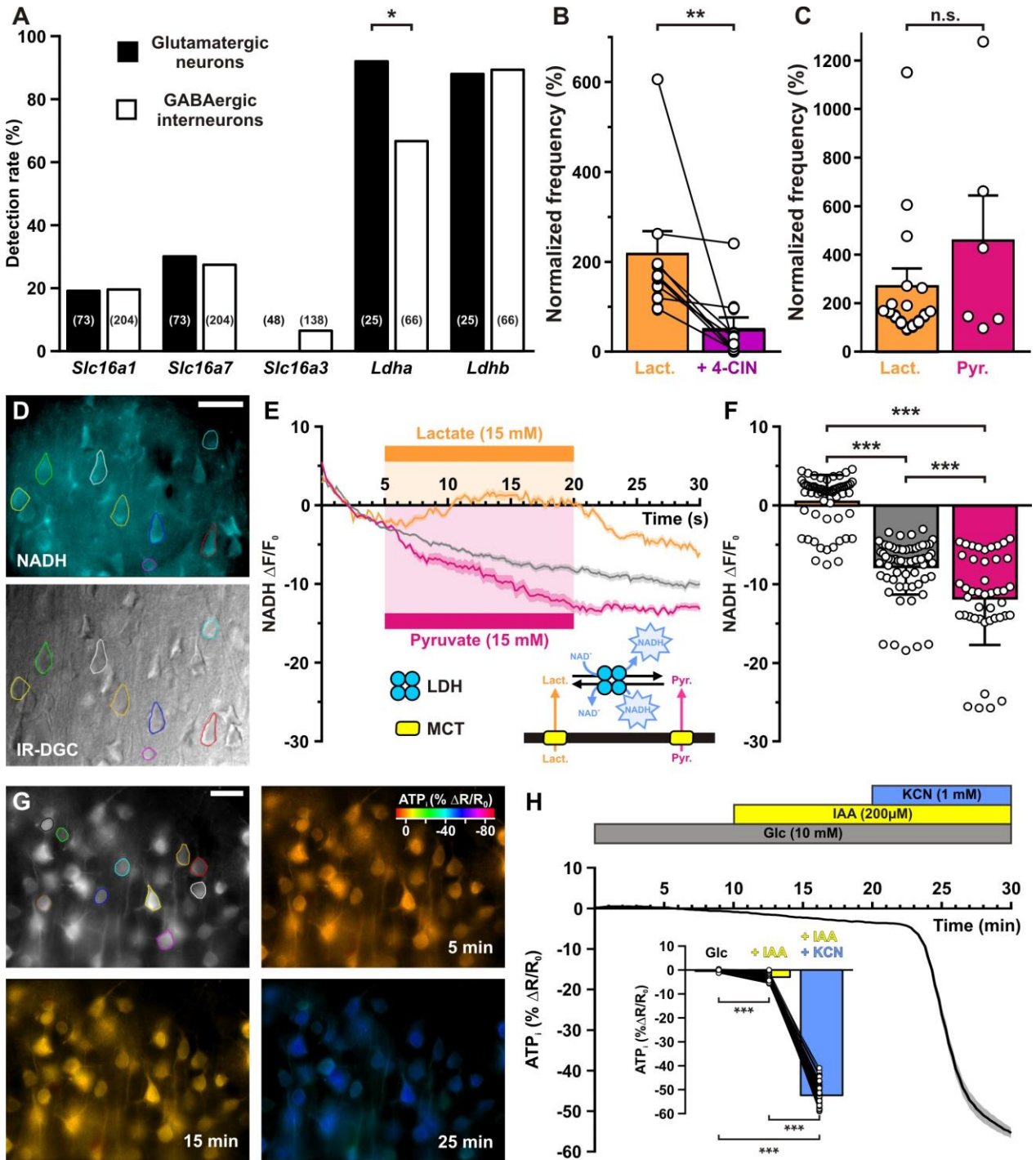
1081 (E) Histograms summarizing the enhancement of normalized frequency by 15 mM
1082 lactate in *Kcnj11*^{+/+} (orange) and *Kcnj11*^{-/-} (pale orange) mouse cortical neurons. The
1083 dash line indicates the normalized mean firing frequency in absence of lactate. Data
1084 are expressed as mean \pm s.e.m., and the individual data points are depicted.

1085 (F) Diagram depicting the enhancement of neuronal activity by lactate via modulation
1086 of K_{ATP} channels.

1087

1088
1089

Figure 6. Lactate enhancement of cortical neuronal activity involves lactate uptake and metabolism.



1090
1091

1092 (A) Histograms summarizing the detection rate of the monocarboxylate transporters
1093 *Slc16a1*, 7 and 3 and *Ldha* and *b* lactate dehydrogenase subunits in glutamatergic
1094 neurons (black) and GABAergic interneurons (white). The numbers in brackets
1095 indicate the number of analyzed cells.

1096 (B) Histograms summarizing the enhancement of normalized frequency by 15 mM
1097 lactate (orange) and its suppression by the MCTs inhibitor 4-CIN (purple). Data are
1098 expressed as mean \pm s.e.m., and the individual data points are depicted.

1099 (C) Histograms summarizing the enhancement of normalized frequency by 15 mM
1100 lactate (orange) and pyruvate (magenta). Data are expressed as mean \pm s.e.m., and
1101 the individual data points are depicted n.s. not statistically significant.

1102 (D) Widefield NADH autofluorescence (upper panel, scale bar: 20 μ m) and
1103 corresponding field of view observed under IR-DGC (lower panel). The somatic
1104 regions of interest are delineated.

1105 (E) Mean relative changes in NADH autofluorescence in control condition (grey) and
1106 in response to 15 mM lactate (orange) or pyruvate (magenta). The colored bars
1107 indicate the duration of applications. Data are expressed as mean \pm s.e.m. Inset:
1108 diagram depicting the NADH changes induced by lactate and pyruvate uptake by
1109 MCT and their interconversion by LDH.

1110 (F) Histograms summarizing the mean relative changes in NADH autofluorescence
1111 measured during the last 5 minutes of 15 mM lactate (orange) or pyruvate (magenta)
1112 application and corresponding time in control condition (grey). Data are expressed as
1113 mean \pm s.e.m., and the individual data points are depicted.

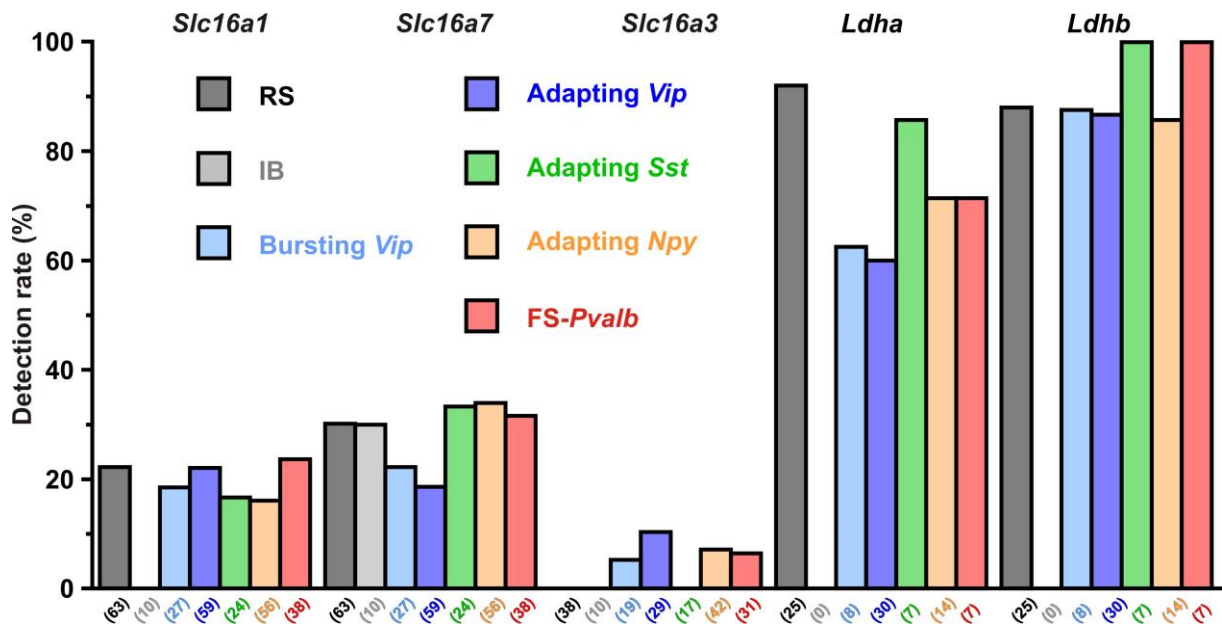
1114 (G) Widefield YFP fluorescence of the ATP biosensor AT1.03^{YEMK} (upper left panel,
1115 scale bar: 30 μ m) and pseudocolor images showing the intracellular ATP (YFP/CFP
1116 ratio value coded by pixel hue, see scale bar in upper right panel) and the
1117 fluorescence intensity (coded by pixel intensity) at different times under 10 mM
1118 extracellular glucose (upper right panel) and after addition of IAA (lower left panel)
1119 and KCN (lower right panel).

1120 (H) Mean relative changes in intracellular ATP (relative YFP/CFP ratio) measured
1121 under 10 mM extracellular glucose (grey) and after addition of IAA (yellow) and KCN
1122 (blue). Data are expressed as mean \pm s.e.m. The colored bars indicate the time and
1123 duration of metabolic inhibitor application. Inset: Histograms summarizing the mean
1124 relative changes in intracellular ATP (relative YFP/CFP ratio) ratio under 10 mM
1125 extracellular glucose (grey) and after addition of IAA (yellow) and KCN (blue). Data
1126 are expressed as mean \pm s.e.m., and the individual data points are depicted.

1127

1128

1129 **Figure 6-figure supplement 1. Detection rate of monocarboxylate transporters**
 1130 **and lactate dehydrogenase subunits in different cortical neuronal types.**

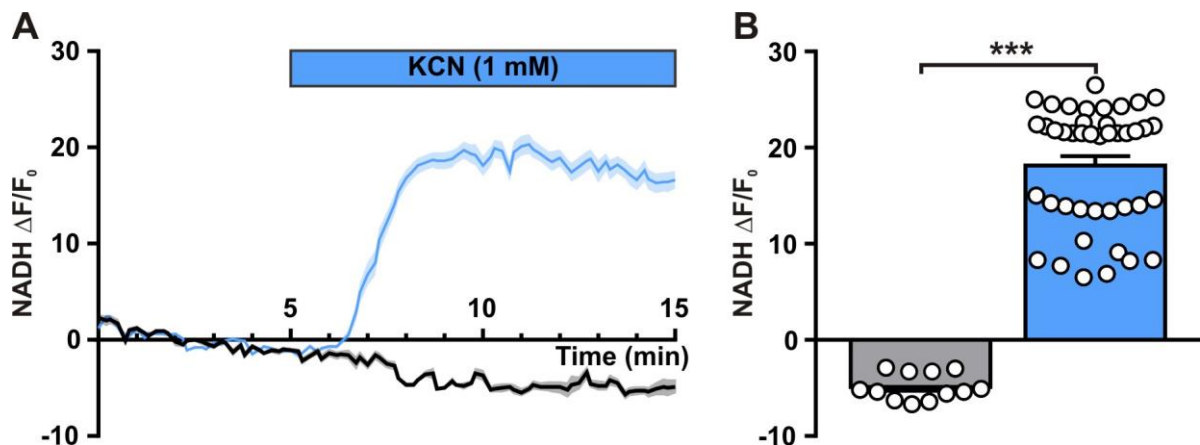


1131
1132

1133 Histograms summarizing the detection rate of the monocarboxylate transporters
 1134 *Slc16a1*, *7* and *3* and *Ldha* and *b* lactate dehydrogenase subunits in different
 1135 neuronal subtypes. The numbers in brackets indicate the number of analyzed cells.

1136

1137 **Figure 6-figure supplement 2. Neuronal NADH autofluorescence increase by**
 1138 **blockade of oxidative phosphorylation.**



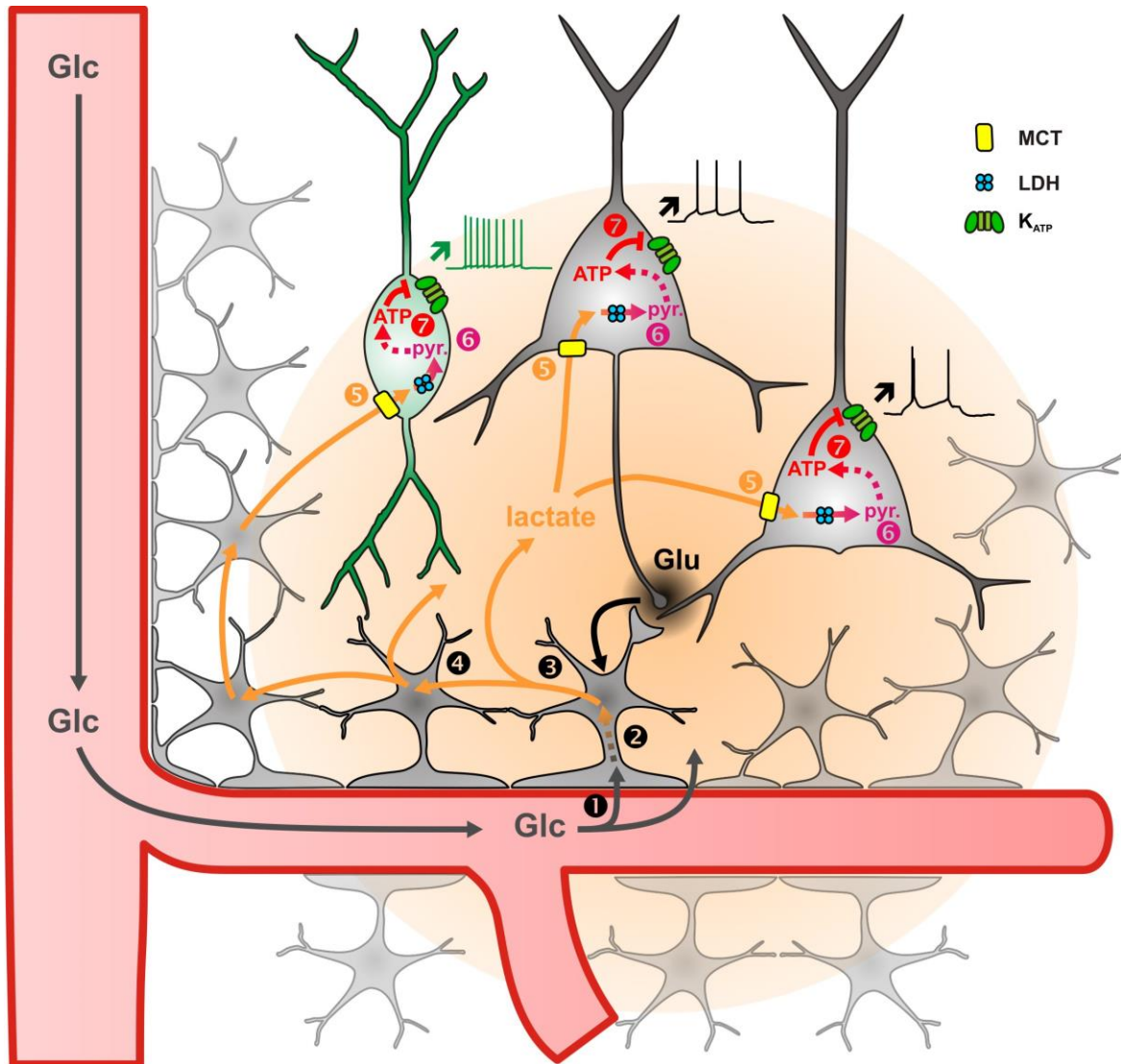
1139
1140

1141 (A) Mean relative changes in NADH autofluorescence in control condition (grey) and
 1142 in response to 1 mM KCN (blue). The colored bar indicates the duration of KCN
 1143 applications. Data are expressed as mean \pm s.e.m.

1144 (B) Histograms summarizing the mean relative changes in NADH autofluorescence
1145 measured during the last 5 minutes of 1 mM KCN application (blue) and
1146 corresponding time in control condition (grey). Data are expressed as mean \pm s.e.m.,
1147 and the individual data points are depicted.

1148

1149 **Figure 7. Diagram summarizing the mechanism of lactate-sensing in the**
 1150 **cortical network.**



1151
 1152 Glutamate (Glu) released during synaptic transmission stimulates **1** blood glucose
 1153 (Glc) uptake in astrocytes, **2** aerobic glycolysis, **3** lactate release and **4** diffusion
 1154 through the astrocytic network. Lactate is then **5** taken up by neurons via
 1155 monobarboxylate transporters (MCT) and **6** oxidized into pyruvate by lactate
 1156 dehydrogenase (LDH). The ATP produced by pyruvate oxidative metabolism **7**
 1157 closes K_{ATP} channels and increases the spiking activity of both pyramidal cells (black)
 1158 and inhibitory interneurons (green). The color gradient of the circles represents the
 1159 extent of glutamate (black) and lactate (orange) diffusion, respectively. Dashed
 1160 arrows indicate multisteps reactions.

1161

1162 **Supplementary file legends**

1163 **Supplementary file 1. Somatic properties of different neuronal types**

1164 n, number of cells, < significantly smaller with $P \leq 0.05$; << significantly smaller with $P \leq 0.01$; <<< significantly smaller with $P \leq 0.001$. n.s. not statistically significant.

1165
1166
1167 **Supplementary file 2. Detection rate of molecular markers in different neuronal types**

1168
1169 Detection rates are given in %; n, number of cells; > significantly larger with $P \leq 0.05$;
1170 >> significantly larger with $P \leq 0.01$; >>> significantly larger with $P \leq 0.001$. n.s. not
1171 statistically significant.

1172

1173 **Supplementary file 3. Passive properties of different neuronal types**

1174 n, number of cells, < significantly smaller with $P \leq 0.05$; << significantly smaller with $P \leq 0.01$; <<< significantly smaller with $P \leq 0.001$.

1175
1176

1177 **Supplementary file 4. Just above threshold properties of different neuronal types**

1178
1179 n, number of cells; < significantly smaller with $P \leq 0.05$; << significantly smaller with $P \leq 0.01$; <<< significantly smaller with $P \leq 0.001$.

1180
1181

1182 **Supplementary file 5. Firing properties of different neuronal types**

1183 n, number of cells; < significantly smaller with $P \leq 0.05$; << significantly smaller with $P \leq 0.01$; <<< significantly smaller with $P \leq 0.001$.

1184
1185

1186 **Supplementary file 6. Action potentials properties of different neuronal types**

1187 n, number of cells; < significantly smaller with $P \leq 0.05$; << significantly smaller with $P \leq 0.01$; <<< significantly smaller with $P \leq 0.001$.

1188
1189

1190 **Supplementary file 7. AH and AD properties of different neuronal types**

1191 n, number of cells; < significantly smaller with $P \leq 0.05$; << significantly smaller with $P \leq 0.01$; <<< significantly smaller with $P \leq 0.001$.

1192
1193

1194 **Source data legends**

1195 **Figure 1-source data 1.**

1196 Somatic, electrophysiological and molecular properties of the cortical neurons shown
1197 in Figure 1A-D.

1198

1199 **Figure 1-source data 2.**

1200 Original file of the full raw unedited gel shown in Figure 1E.

1201

1202 **Figure 1-source data 3.**

1203 Uncropped gel shown in Figure 1E with relevant bands labelled.

1204

1205 **Figure 1-source data 4.**

1206 Statistical comparisons of the detection of K_{ATP} channel subunits in different types of
1207 cortical neurons shown in Figure 1F.

1208

1209 **Figure 1-figure supplement 1-source data 1.**

1210 Original file of the full raw unedited gel shown in Figure 1-figure supplement 1A.
1211
1212 **Figure 1-figure supplement 1-source data 2.**
1213 Uncropped gel shown in Figure 1-figure supplement 1A with relevant lanes labelled.
1214 Yellow rectangles denote bands of the expected size.
1215
1216 **Figure 1-figure supplement 1-source data 3.**
1217 Original file of the full raw unedited gel shown in Figure 1-figure supplement 1B.
1218
1219 **Figure 1-figure supplement 1-source data 4.**
1220 Uncropped gel shown in Figure 1-figure supplement 1B with relevant bands labelled.
1221
1222 **Figure 2-source data 1.**
1223 Statistical analyses of whole cell current and membrane resistance changes induced
1224 by K_{ATP} channel modulators (shown in Figure 2C insets).
1225
1226 **Figure 2-source data 2.**
1227 Statistical comparisons of K_{ATP} current reversal potential and relative K_{ATP}
1228 conductance between neuronal subtypes and groups (shown in Figure 2E-H) and of
1229 whole-cell K_{ATP} conductance and current density (shown in Figure 2-figure
1230 supplement 2).
1231
1232 **Figure 2-figure supplement 1-source data**
1233 Statistical analyses of the effect of MnTMPyP on normalized K_{ATP} currents and
1234 conductance whole-cell K_{ATP} conductance (shown in Figure 2-figure supplement 2B-C).
1235
1236 **Figure 3-source data 2.**
1237 Molecular profile of layer II-III pyramidal neurons shown in Figure 3B.
1238
1239 **Figure 3-source data 2.**
1240 Statistical analysis of whole-cell ATP washout currents in $Kcnj11^{+/+}$
1241 and $Kcnj11^{-/-}$ cortical neurons (shown in Figure 3G).
1242
1243 **Figure 4-source data 1.**
1244 Statistical analyses of membrane potential, membrane resistance and firing rate
1245 changes induced by K_{ATP} channel modulators (shown in Figure 4D-E).
1246
1247 **Figure 4-source data 2.**
1248 Statistical comparisons between neuronal subtypes and groups of the effect K_{ATP}
1249 channel modulators on membrane potential, membrane resistance (shown in Figure
1250 4 G-J) and firing rate (shown in Figure 4-figure supplement 1 C,D) as well as of the
1251 proportion of responsive neurons (shown in Figure 4-figure supplement 1 A,B).
1252
1253 **Figure 5-source data 1.**
1254 Statistical analysis of the effect of glucose and lactate on firing rate (shown in Figure
1255 5B).
1256
1257 **Figure 5-source data 2.**
1258 Statistical analysis of dose-dependent enhancement of firing frequency by lactate
1259 (shown in Figure 5C).

1260
1261 **Figure 5-source data 3.**
1262 Statistical analysis of the effect of diazoxide and tolbutamide on firing rate
1263 enhancement by lactate (shown in Figure 5D).
1264
1265 **Figure 5-source data 4.**
1266 Statistical comparison of lactate enhancement of normalized frequency in *Kcnj11*^{+/+}
1267 and *Kcnj11*^{-/-} (shown in Figure 5E).
1268
1269 **Figure 6-source data 1.**
1270 Statistical comparisons of the detection rate of monocarboxylate transporters and
1271 lactate dehydrogenase subunits between neuronal groups (shown in Figure 6A) and
1272 subtypes (shown in Figure 6-figure supplement 1).
1273
1274 **Figure 6-source data 2.**
1275 Statistical analysis of the effect of MCT inhibition by 4-CIN on lactate enhanced firing
1276 rate (shown in Figure 6B).
1277
1278 **Figure 6-source data 3.**
1279 Statistical comparison of the relative effect of lactate and pyruvate on firing rate
1280 enhancement (shown in Figure 6C).
1281
1282 **Figure 6-source data 4.**
1283 Statistical comparisons of the relative effects of lactate, pyruvate and control condition
1284 on the the mean relative changes in NADH autofluorescence (shown in Figure 6F).
1285
1286 **Figure 6-source data 5.**
1287 Statistical analysis of the effects of IAA and KCN on the relative changes in
1288 intracellular ATP (shown in Figure 6H inset).
1289
1290 **Figure 6-figure supplement 2-source data**
1291 Statistical analysis of effect of KCN on the mean relative changes in NADH
1292 autofluorescence (shown in Figure 6-figure supplement 2B).
1293
1294 **Supplementary file 1-source data.**
1295 Statistical comparisons of somatic properties in different neuronal types.
1296
1297 **Supplementary file 2-source data.**
1298 Statistical comparisons of detection rate of molecular markers in different neuronal
1299 types.
1300
1301 **Supplementary file 3-source data.**
1302 Statistical comparisons of passive properties in different neuronal types.
1303
1304 **Supplementary file 4-source data.**
1305 Statistical comparisons of just above threshold properties in different neuronal types.
1306
1307 **Supplementary file 5-source data.**
1308 Statistical comparisons of firing properties in different neuronal types.
1309

1310 **Supplementary file 6-source data.**
1311 Statistical comparisons of action potentials properties in different neuronal types.
1312
1313 **Supplementary file 7-source data.**
1314 Statistical comparisons of AH and AD properties in different neuronal types.
1315
1316

1317 **References**

1318

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Key Resources Table				
Reagent type (species) or resource	Designation	Source or reference	Identifiers	Additional information
strain, strain background (<i>Rattus norvegicus</i> , Wistar, male)	Wistar	Janvier Labs	jHan:WI	
strain, strain background (<i>Mus musculus</i> , C57BL/6RJ, male and female)	Wild type, <i>Kcnj11</i> ^{+/+}	Janvier Labs	C57BL/6 RJ	
strain, strain background (<i>Mus musculus</i> , B6.129P2, male and female)	B6.129P2- <i>Kcnj11</i> ^{tm1Sse} , <i>Kcnj11</i> ^{-/-}	PMID: 9724715 (Miki et al., 1998)	RRID: MGI:5433111	
cell line (<i>Mesocricetus auratus</i>)	BHK-21 clone 13 (baby hamster kidneys fibroblasts)	ATCC	CCL-10, RRID: CVCL_1915	
recombinant DNA reagent	pcDNA-ATeam1.03YEM K (plasmid)	PMID: 19720993 (Imamura et al., 2009)		
recombinant DNA reagent	pSinRep5 (plasmid)	Invitrogen	K750-01	
recombinant DNA reagent	pDH(26S) (helper plasmid)	Invitrogen	K750-01	
sequence-based reagent	rat <i>Slc17a7</i> external sense	PMID: 16339088 (Gallopín et al., 2006)	PCR primers	GGCTCCTTTT TCTGGGGGT AC
sequence-based reagent	rat <i>Slc17a7</i> external antisense	PMID: 16339088 (Gallopín et al., 2006)	PCR primers	CCAGCCGAC TCCGTTCTAA G

sequence-based reagent	rat <i>Slc17a7</i> internal sense	PMID: 16339088 (Gallopín et al., 2006)	PCR primers	TGGGGGTAC ATTGTCCTC AGA
sequence-based reagent	rat <i>Slc17a7</i> internal antisense	PMID: 16339088 (Gallopín et al., 2006)	PCR primers	ATGGCAAGC AGGGTATGT GAC
sequence-based reagent	rat/mouse <i>Gad2</i> external sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	CCAAAAGTTC ACGGGCGG
sequence-based reagent	rat/mouse <i>Gad2</i> external antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	TCCTCCAGAT TTTGCGGTTG
sequence-based reagent	rat <i>Gad2</i> internal sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	TGAGAAGCC AGCAGAGAG CG
sequence-based reagent	rat <i>Gad2</i> internal antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	TGGGGTAAT GGAAATCAAT CACTT
sequence-based reagent	rat <i>Gad1</i> external sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	ATGATACTTG GTGTGGCGT AGC
sequence-based reagent	rat <i>Gad1</i> external antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	GTTTGCTCCT CCCCGTTCTT AG
sequence-based reagent	rat <i>Gad1</i> internal sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	CAATAGCCTG GAAGAGAAG AGTCG
sequence-based reagent	rat <i>Gad1</i> internal antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	GTTTGCTCCT CCCCGTTCTT AG

sequence-based reagent	rat <i>Nos1</i> external sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	CCTGGGGCT CAAATGGTAT G
sequence-based reagent	rat <i>Nos1</i> external antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	CACAATCCAC ACCCAGTCG G
sequence-based reagent	rat <i>Nos1</i> internal sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	CCTCCCCGC TGTGTCCAA
sequence-based reagent	rat <i>Nos1</i> internal antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	GAGTGGTGG TCAACGATG GTCA
sequence-based reagent	rat <i>Calb1</i> external sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	GAAAGAAGG CTGGATTGGA G
sequence-based reagent	rat <i>Calb1</i> external antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	CCCACACATT TTGATTCCCT G
sequence-based reagent	rat <i>Calb1</i> internal sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	ATGGGCAGA GAGATGATG GG
sequence-based reagent	rat <i>Calb1</i> internal antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	TATCATCCAC GGTCTTGTTT GC
sequence-based reagent	rat <i>Pvalb</i> external sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	GCCTGAAGA AAAAGAGTG CGG
sequence-based reagent	rat <i>Pvalb</i> external antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	GTCCCCGTC CTTGTCTCCA G

sequence-based reagent	rat <i>Pvalb</i> internal sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	GCGGATGAT GTGAAGAAG GTG
sequence-based reagent	rat <i>Pvalb</i> internal antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	CAGCCATCA GCGTCTTTGT T
sequence-based reagent	rat <i>Calb2</i> external sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	TTGATGCTGA CGGAAATGG GTA
sequence-based reagent	rat <i>Calb2</i> external antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	CAAGCCTCC ATAAACTCAG CG
sequence-based reagent	rat <i>Calb2</i> internal sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	GCTGGAGAA GGCAAGGAA AGG
sequence-based reagent	rat <i>Calb2</i> internal antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	ATTCTCTTCG GTTGGCAGG A
sequence-based reagent	rat <i>Npy</i> external sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	CGAATGGGG CTGTGTGGA
sequence-based reagent	rat <i>Npy</i> external antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	AGTTTCATTT CCCATCACCA CAT
sequence-based reagent	rat <i>Npy</i> internal sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	CCCTCGCTCT ATCCCTGCTC
sequence-based reagent	rat <i>Npy</i> internal antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	GTTCTGGGG GCATTTTCTG TG

sequence-based reagent	rat <i>Vip</i> external sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	TTATGATGTG TCCAGAAATG CGAG
sequence-based reagent	rat <i>Vip</i> external antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	TTTTATTTGG TTTTGCTATG GAAG
sequence-based reagent	rat <i>Vip</i> internal sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	TGGCAAACG AATCAGCAGT AGC
sequence-based reagent	rat <i>Vip</i> internal antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	GAATCTCCCT CACTGCTCCT CT
sequence-based reagent	rat <i>Sst</i> external sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	ATGCTGTCCT GCCGTCTCC A
sequence-based reagent	rat <i>Sst</i> external antisense	PMID: 17068095 (Férézou et al., 2007)	PCR primers	GCCTCATCTC GTCCTGCTCA
sequence-based reagent	rat <i>Sst</i> internal sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	GCATCGTCCT GGCTTTGGG
sequence-based reagent	rat <i>Sst</i> internal antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	AGGCTCCAG GGCATCGTTC T
sequence-based reagent	rat <i>Cck</i> external sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	TGTCTGTGCG TGGTGATGG C
sequence-based reagent	rat <i>Cck</i> external antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	GCATAGCAA CATTAGGTCT GGGAG

sequence-based reagent	rat <i>Cck</i> internal sense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	ATACATCCAG CAGGTCCGC AA
sequence-based reagent	rat <i>Cck</i> internal antisense	PMID: 19295167 (Karagiannis et al., 2009)	PCR primers	GGTCGTGTG CGTGGTTGTT T
sequence-based reagent	rat <i>Kcnj8</i> external sense	This paper	PCR primers	CTGGCTCACA AGAACATCC G
sequence-based reagent	rat <i>Kcnj8</i> external antisense	This paper	PCR primers	AGCGTCTCTG CCCTTCTGTG
sequence-based reagent	rat <i>Kcnj8</i> internal sense	PMID: 26156991 (Varin et al., 2015)	PCR primers	GCTGGCTGC TCTTCGCTAT C
sequence-based reagent	rat <i>Kcnj8</i> internal antisense	This paper	PCR primers	TTCTCCCTCC AAACCCAATG
sequence-based reagent	rat <i>Kcnj11</i> external sense	This paper	PCR primers	CCCCACACG CTGCTCATTT T
sequence-based reagent	rat <i>Kcnj11</i> external antisense	This paper	PCR primers	AGGAGCCAG GTCGTAGAG CG
sequence-based reagent	rat <i>Kcnj11</i> internal sense	This paper	PCR primers	GCGTCACAA GCATCCACTC C
sequence-based reagent	rat <i>Kcnj11</i> internal antisense	This paper	PCR primers	CCACCCACA CCGTTCTCCA T

sequence-based reagent	rat <i>Abcc8</i> external sense	This paper	PCR primers	GGTGAAGAA GCCTCCGAT GA
sequence-based reagent	rat <i>Abcc8</i> external antisense	This paper	PCR primers	GGTGAAGAA GCCTCCGAT GA
sequence-based reagent	rat <i>Abcc8</i> internal sense	This paper	PCR primers	GGTTCGGTC CACTGTCAAG G
sequence-based reagent	rat <i>Abcc8</i> internal antisense	This paper	PCR primers	GTCAGCGTCT CCATCCGTG C
sequence-based reagent	rat <i>Abcc9</i> external sense	This paper	PCR primers	CGCTGCCTTT TGAGTCCTGT
sequence-based reagent	rat <i>Abcc9</i> external antisense	This paper	PCR primers	GATGGCAAG GAGGAGAGA CG
sequence-based reagent	rat <i>Abcc9</i> internal sense	This paper	PCR primers	TGGACAACCTA CGAGCAGGC G
sequence-based reagent	rat <i>Abcc9</i> internal antisense	This paper	PCR primers	CACAACCCA CCTGACCCA CA
sequence-based reagent	rat <i>Sst</i> intron external sense	PMID: 17267760 (Hill et al., 2007)	PCR primers	GGAAATGGC TGGGACTCG TC
sequence-based reagent	rat <i>Sst</i> intron external antisense	PMID: 17267760 (Hill et al., 2007)	PCR primers	AAACCATGGA TGATAGGAA GTCGT

sequence-based reagent	rat <i>Sst</i> intron internal sense	This paper	PCR primers	GTCCCCTTTG CGAATTCCT
sequence-based reagent	rat <i>Sst</i> intron antisense	This paper	PCR primers	TTCGAGCAG CTCCATTTTC C
sequence-based reagent	rat SUR2A/B sense	This paper	PCR primers	ACTTCAGCGT TGGACAGAG ACA
sequence-based reagent	rat SUR2A/B antisense	This paper	PCR primers	GGTCAGCAG TCAGAATGGT GTG
sequence-based reagent	mouse <i>Slc17a7</i> external sense	PMID: 23565079 (Cabezas et al., 2013)	PCR primers	GGCTCCTTTT TCTGGGGCT AC
sequence-based reagent	mouse <i>Slc17a7</i> external antisense	PMID: 23565079 (Cabezas et al., 2013)	PCR primers	CCAGCCGAC TCCGTTCTAA G
sequence-based reagent	mouse <i>Slc17a7</i> internal sense	PMID: 23565079 (Cabezas et al., 2013)	PCR primers	ATTCGCAGCC AACAGGGTC T
sequence-based reagent	mouse <i>Slc17a7</i> internal antisense	PMID: 23565079 (Cabezas et al., 2013)	PCR primers	TGGCAAGCA GGGTATGTG AC
sequence-based reagent	mouse <i>Gad2</i> external sense	PMID: 22754499 (Perrenoud et al., 2012)	PCR primers	CCAAAAGTTC ACGGGCGG
sequence-based reagent	mouse <i>Gad2</i> external antisense	PMID: 22754499 (Perrenoud et al., 2012)	PCR primers	TCCTCCAGAT TTTGCGGTTG

sequence-based reagent	mouse <i>Gad2</i> internal sense	PMID: 22754499 (Perrenoud et al., 2012)	PCR primers	CACCTGCGA CCAAAAACCC T
sequence-based reagent	mouse <i>Gad2</i> internal antisense	PMID: 22754499 (Perrenoud et al., 2012)	PCR primers	GATTTTGC GG TTGGTCTGCC
sequence-based reagent	mouse <i>Gad1</i> external sense	PMID: 12196560 (F��rezou et al., 2002)	PCR primers	TACGGGGTT CGCACAGGT C
sequence-based reagent	mouse <i>Gad1</i> external antisense	PMID: 23565079 (Cabezas et al., 2013)	PCR primers	CCCAGGCAG CATCCACAT
sequence-based reagent	mouse <i>Gad1</i> internal sense	PMID: 23565079 (Cabezas et al., 2013)	PCR primers	CCCAGAAGT GAAGACAAAA GGC
sequence-based reagent	mouse <i>Gad1</i> internal antisense	PMID: 23565079 (Cabezas et al., 2013)	PCR primers	AATGCTCCGT AAACAGTCGT GC
sequence-based reagent	mouse <i>Atp1a1</i> external sense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	CAGGGCAGT GTTTCAGGCT AA
sequence-based reagent	mouse <i>Atp1a1</i> external antisense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	CCGTGGAGA AGGATGGAG C
sequence-based reagent	mouse <i>Atp1a1</i> internal sense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	TAAGCGGGC AGTAGCGGG
sequence-based reagent	mouse <i>Atp1a1</i> internal antisense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	AGGTGTTTGG GCTCAGATG C

sequence-based reagent	mouse <i>Atp1a2</i> external sense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	AGTGAGGAA GATGAGGGA CAGG
sequence-based reagent	mouse <i>Atp1a2</i> external antisense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	ACAGAAGCC CAGCACTCGT T
sequence-based reagent	mouse <i>Atp1a2</i> internal sense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	AAATCCCCTT CAACTCCACC A
sequence-based reagent	mouse <i>Atp1a2</i> internal antisense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	GTTCCCCAAG TCCTCCCAGC
sequence-based reagent	mouse <i>Atp1a3</i> external sense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	CGGAAATACA ATACTGACTG CGTG
sequence-based reagent	mouse <i>Atp1a3</i> external antisense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	GTCATCCTCC GTCCCTGCC
sequence-based reagent	mouse <i>Atp1a3</i> internal sense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	TGACACACA GTAAAGCCC AGGA
sequence-based reagent	mouse <i>Atp1a3</i> internal antisense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	CCACAGCAG GATAGAGAA GCCA
sequence-based reagent	mouse <i>Kcnj11</i> external sense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	CGGAGAGGG CACCAATGT
sequence-based reagent	mouse <i>Kcnj11</i> external antisense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	CACCCACGC CATTCTCCA

sequence-based reagent	mouse <i>Kcnj11</i> internal sense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	CATCCACTCC TTTTCATCTG CC
sequence-based reagent	mouse <i>Kcnj11</i> internal antisense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	TCGGGGCTG GTGGTCTTG
sequence-based reagent	mouse <i>Abcc8</i> external sense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	CAGTGTGCC CCCCGAGAG
sequence-based reagent	mouse <i>Abcc8</i> external antisense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	GGTCTTCTCC CTCGCTGTCT G
sequence-based reagent	mouse <i>Abcc8</i> internal sense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	ATCATCGGA GGCTTCTTCA CC
sequence-based reagent	mouse <i>Abcc8</i> internal antisense	PMID: 29985318 (Devienne et al., 2018)	PCR primers	GGTCTTCTCC CTCGCTGTCT G
sequence-based reagent	mouse <i>Sst</i> intron external sense	PMID: 12930808 (Thoby-Brisson et al., 2003)	PCR primers	CTGTCCCCCT TACGAATCCC
sequence-based reagent	mouse <i>Sst</i> intron external antisense	PMID: 12930808 (Thoby-Brisson et al., 2003)	PCR primers	CCAGCACCA GGGATAGAG CC
sequence-based reagent	mouse <i>Sst</i> intron internal sense:	PMID: 20427660 (Cea-del Rio et al., 2010)	PCR primers	CTTACGAATC CCCCAGCCTT
sequence-based reagent	mouse <i>Sst</i> intron internal antisense	PMID: 20427660 (Cea-del Rio et al., 2010)	PCR primers	TTGAAAGCCA GGGAGGAAC T

sequence-based reagent	rat <i>Slc16a1</i> external sense	This paper	PCR primers	GTCAGCCTTC CTCCTTTCCA
sequence-based reagent	rat <i>Slc16a1</i> external antisense	This paper	PCR primers	TCCGCTTTCT GTTCTTTGGC
sequence-based reagent	rat <i>Slc16a1</i> internal sense	This paper	PCR primers	TTGTTGCGAA TGGAGTGTG C
sequence-based reagent	rat <i>Slc16a1</i> internal antisense	This paper	PCR primers	CACGCCACA AGCCCAGTAT G
sequence-based reagent	rat <i>Slc16a7</i> external sense	This paper	PCR primers	GCGAAGTCT AAAAGTAAGG TTGGC
sequence-based reagent	rat <i>Slc16a7</i> external antisense	This paper	PCR primers	ATTTACCAGC CAGGGGAGG G
sequence-based reagent	rat <i>Slc16a7</i> internal sense	This paper	PCR primers	CCGTATGCTA AGGACAAAG GAGT
sequence-based reagent	rat <i>Slc16a7</i> internal antisense	This paper	PCR primers	GGGAAGAAC TGGGCAACA CT
sequence-based reagent	rat <i>Slc16a3</i> external sense	This paper	PCR primers	CATTGGTCTC GTGCTGCTGT
sequence-based reagent	rat <i>Slc16a3</i> external antisense	This paper	PCR primers	CCCCGTTTTT CTCAGGCTCT

sequence-based reagent	rat <i>Slc16a3</i> internal sense	This paper	PCR primers	TGTGGCTGT GCTCATCGG AC
sequence-based reagent	rat <i>Slc16a3</i> internal antisense	This paper	PCR primers	CCTCTTCCTC TTCCCGATGC
sequence-based reagent	rat <i>Ldha</i> external sense	This paper	PCR primers	GAAGAACAG GTCCCCCAG AA
sequence-based reagent	rat <i>Ldha</i> external antisense	This paper	PCR primers	GGGTTTGAG ACGATGAGC AGT
sequence-based reagent	rat <i>Ldha</i> internal sense	This paper	PCR primers	CAGTTGTTGG GGTTGGTGCT T
sequence-based reagent	rat <i>Ldha</i> internal antisense	This paper	PCR primers	TCTCTCCCTC TTGCTGACG G
sequence-based reagent	rat <i>Ldhb</i> external sense	This paper	PCR primers	ACTGCCGTC CCGAACAAC AA
sequence-based reagent	rat <i>Ldhb</i> external antisense	This paper	PCR primers	ACTCTCCCCC TCCTGCTGG
sequence-based reagent	rat <i>Ldhb</i> internal sense	This paper	PCR primers	TCTGGGGAA GTCTCTGGCT GA
sequence-based reagent	rat <i>Ldhb</i> internal antisense	This paper	PCR primers	TTGGCTGTCA CGGAGTAAT CTTT

commercial assay or kit	MEGAscript™ SP6 Transcription Kit	Ambion	AM1330	
chemical compound, drug	Pinacidil monohydrate	Sigma-Aldrich	P154	
chemical compound, drug	Diazoxide	Sigma-Aldrich	D9035	
chemical compound, drug	Tolbutamide	Sigma-Aldrich	T0891	
chemical compound, drug	Mn(III)tetrakis(1-methyl-4-pyridyl)porphyrin	Millipore	475872	
chemical compound, drug	Gramicidin from Bacillus aneurinolyticus (Bacillus brevis)	Sigma-Aldrich	G5002	
chemical compound, drug	Sodium L-lactate	Sigma-Aldrich	L7022	
chemical compound, drug	α -Cyano-4-hydroxycinnamic Acid	Sigma-Aldrich	C2020	
chemical compound, drug	Sodium pyruvate	Sigma-Aldrich	P2256	
chemical compound, drug	Sodium iodoacetate	Sigma-Aldrich	I2512	

chemical compound, drug	Potassium cyanide	Sigma-Aldrich	60178	
chemical compound, drug	Dithiothreitol	VWR	443852A	
chemical compound, drug	Primer "random"	Roche	1103473100 1	
chemical compound, drug	dNTPs	GE Healthcare Life Sciences	28-4065- 52	
chemical compound, drug	Mineral Oil	Sigma- Aldrich	M5904	
chemical compound, drug	RNasin Ribonuclease Inhibitors	Promega	N2511	
chemical compound, drug	SuperScript II Reverse Transcriptase	Invitrogen	18064014	
chemical compound, drug	Taq DNA Polymerase	Qiagen	201205	
chemical compound, drug	Penicillin- Streptomycin	Sigma- Aldrich	P4333- 100ML	
software, algorithm	Pclamp v 10.2	Molecular Devices	RRID: SCR_011 323	

software, algorithm	Matlab v 2018b	MathWorks	RRID: SCR_001 622	
software, algorithm	Statistica v 6.1	Statsoft	RRID: SCR_014 213	
software, algorithm	GraphPad Prism v 7	GraphPad	RRID: SCR_002 798	
software, algorithm	ImagingWorkben ch v 6.0.25	INDEC Systems		
software, algorithm	FIJI	PMID: 22743772 (Schindelin et al., 2012)	RRID: SCR_002 285	
software, algorithm	Image-Pro Analyzer v 7	MediaCybern etics		
other	Vibratome	Leica	VT1000S RRID: SCR_016 495	
other	Upright microscope	Olympus	BX51WI	
other	Dual port module	Olympus	WI-DPMC	
other	60x Objective	Olympus	LUMPlan FI /IR 60x/0.90 W	

other	40x Objective	Olympus	LUMPlan FI /IR 40x/0.80 W	
other	CCD camera	Roper Scientific	CoolSnap HQ2	
other	Axopatch 200B	Molecular Devices	RRID: SCR_0188 66	
other	Digidata 1440A	Molecular Devices	RRID: SCR_0210 38	
other	S900 stimulator	Dagan corporation		
other	pE-2	CoolLED		
other	Dichroic mirror	Semrock	FF395/495 /610-Di01- 25x36	
other	Emission filter	Semrock	FF01- 425/527/68 5-25	
other	780 nm Collimated LED	Thorlabs	M780L3- C1	
other	Dotd Gradient Contrast	Luigs and Neumann	200-100 200 0155	

other	Beam splitter	Semrock	725 DCSPXR	
other	Analogic CCD camera	Sony	XC ST-70 CE	
other	Millicell	Millipore	PICM0R G50	
other	Excitation filter	Semrock	FF02- 438/24-25	
other	Dichroic mirror	Semrock	FF458- Di02- 25x36	
other	Emission filter	Semrock	FF01- 483/32-25	
other	Emission filter	Semrock	FF01- 542/27-25	
other	Filter wheel	Sutter Instruments	Lambda 10B	

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