Supplemental 1: (A) Changes in extracellular pH. $1x10^6$ PMN were plated on 3.0 μM pore inserts in the presence or absence of fMLP and the extracellular pH was recorded

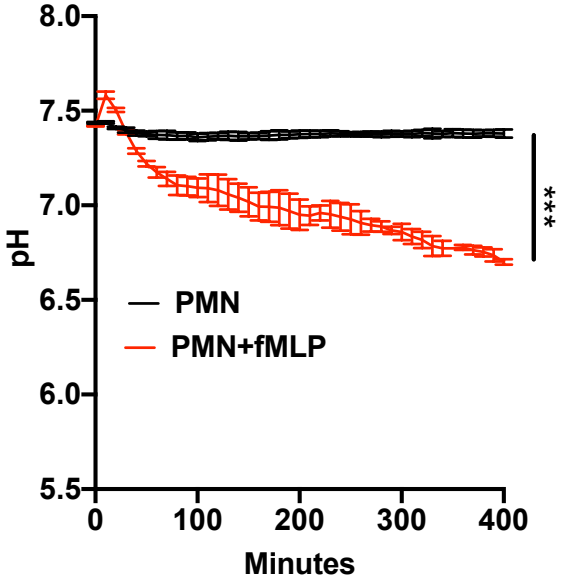
every minute for 400 min. Data are expressed as pH (n=3). (B) Lactate detected in the supernatant from $1x10^6$ PMN in the presence or absence of fMLP (n=3). n=number of independent experiments performed, separate passages of cells were used for each experiment. The data for each experiment was pooled and expressed as the mean ± SEM and p-value determined by ANOVA or T-test, ***p<0.0001

Supplemental 2: (A) Luciferase promoter assay in T84 and Caco2 IECs treated in combination with 100 μM Ado and 1μM of the Ado A2B receptor inhibitor PSB-603 (n=3). (B) Representative western blot and densitometry analysis of SLC26A3 expression following 24 hr 100 μM Ado treatment in T84 IECs pretreated with Erk inhibitor (n=3). n=number of independent experiments performed, separate passages of cells were used for each experiment. The data for each experiment was pooled and expressed as the mean ± SEM and p-value determined by ANOVA or T-test, * p< 0.01, ***p<0.0001,

Supplemental 3: (A) Primer design for site-directed mutagenesis of each CREB site within the SLC26A3 promoter. (B) Sanger sequencing results confirming mutation within the selected CREB sites. (C) Analysis of SLC26A3 promoter activity in CREB mutants in T84 and Caco2 cells treated 100 μM Ado (n=3). n=number of independent experiments performed, separate passages of cells were used for each experiment. The data for each experiment was pooled and expressed as the mean ± SEM and p-value determined by ANOVA or T-test, * p< 0.01

Supplemental 4: Tissue homeostasis and Isc when treated with Ado or forskolin. (A) Basal to apical fluid flux inT84 VC, OE, and KD IECs induced by 24 hr 100 μM Ado (n=3). (B) Basal to apical fluid flux inT84 VC, OE, and KD IECs induced by 24 hr 10 μM forskolin treatment (n=3). (C) Peak Isc in T84 VC, OE, and KD IECs treated apically with 10 or 100 μM Ado (n=3). (D) Peak Isc in T84 VC, OE, and KD IECs treated basally with 10 or 100 μM Ado (n=3). (E) Intracellular pH following treatment with 10 μM forskolin (n=3). (F) qPCR quantification of SLC26A3, cFOS, NR4A2, and NR4A3 expression following a 3 hr treatment with 10 μM forskolin (n=3). n=number of independent experiments performed, separate passages of cells were used for each experiment. The data for each experiment was pooled and expressed as the mean ± SEM and p-value determined by ANOVA or T-test, * $p<0.01$, *** $p<0.0001$

A



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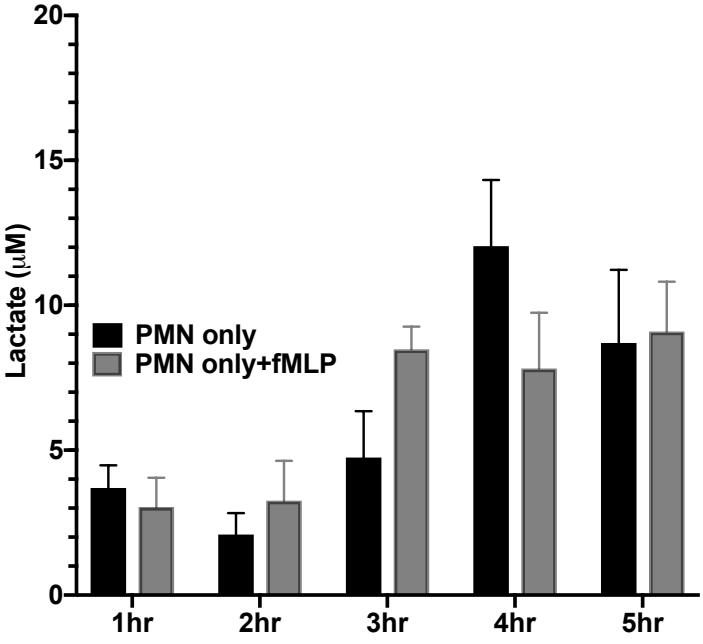
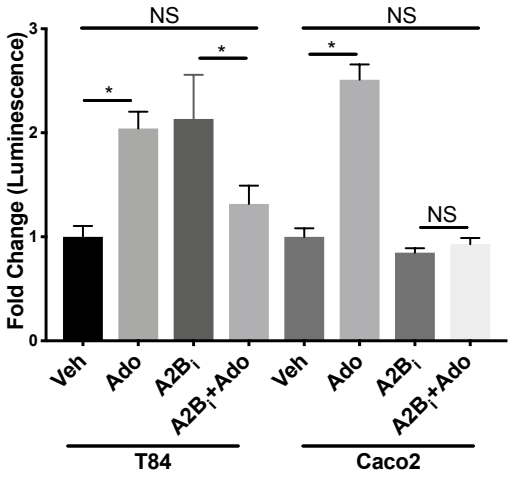


Supplemental 1

A



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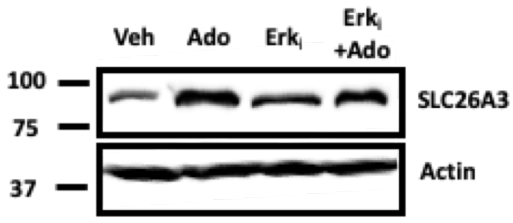

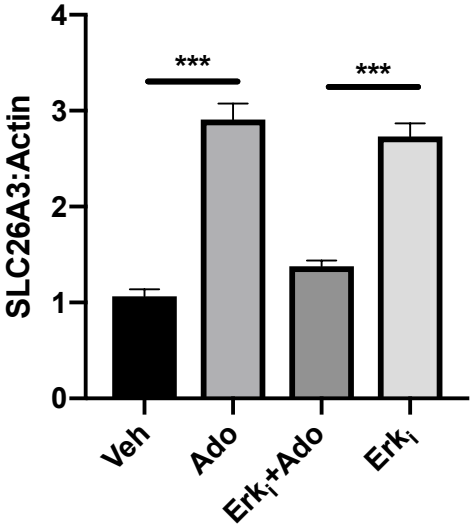

Supplemental 2

Supplemental 3

A

Creb Site	Primer Direction	Primer Sequence
CREB1	Forward	5'-ctaaaaaaaaatttttaacacacttgtttttcacccagccctttttgccaatttctcctctaactctttctttg-3'
	Reverse	5'-caaagaaagagttagaggagaaattggcaaaaagggctgggtgaaaaacaagtgtgttaaaaatttttttttag-3'
CREB2	Forward	5'-cacaatgaatactttcaactctcatccgcattaaaagcatttggcattgctgactacactttc-3'
	Reverse	5'-gaaagtgtagtcagcaatgccaaatgcttttaatgcggatgagagttgaaagtattcattgtg-3'
CREB3	Forward	5'-ttaatgcacttgtgtgtacacgctttcattggtttgcagagattgcacagcagatgct-3'
	Reverse	5'-agcatctgctgtgcaatctctgcaaaccaatgaaagcgtgtacacacaagtgcattaa-3'
CREB4	Forward	5'-tgcatagggatgtctatatataggctatacgcgacagtggacaaattacctttctgtcag-3'
	Reverse	5'-ctgacagaaaggtaatttgtccactgtcgcgtatagcctatatatagacatccctatgca-3'
CREB5	Forward	5'-gtttgcagagattgcacagcagatgccacagtgtacttaaaaaaaaaaagaatcttctcaag-3
	Reverse	5'-cttgagaagattcttttttttttttaagtacacgttggcatctgctgtgcaatctctgcaaac-3'

B

CREB1

```
WT     61   GTTAGAGGAGAAATTGGCAAAAAGGATGAGGTGAAAAACAAGTGTGTTAAAAAttttttt  119
            ||||||||||||||||||||||||||    ||||||||||||||||||||||||||||||
Mut    122  GTTAGAGGAGAAATTGGCAAAAAGGGCTGGGTGAAAAACAAGTGTGTTAAAAATTTTTT  180
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CREB2

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WT     301  AAGAGGAGTTCATGAAAGTGTAGTCAGCAATGCCAAATGCTTTTAAGTAAGATGAGAGTT  360
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Mut    361  AAGAGGAGTTCATGAAAGTGTAGTCAGCAATGCCAAATGCTTTTAATGCGGATGAGAGTT  420
```

CREB3

```
WT     661  TGCTGTGCAATCTCTGCAAACCAATGAAATTACGTACACACAAGTGCATTAAACCACCCA  720
            ||||||||||||||||||||||||||||||    ||||||||||||||||||||||||||||
Mut    726  TGCTGTGCAATCTCTGCAAACCAATGAAAGCGTGTACACACAAGTGCATTAAACCACCCA  785
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CREB4

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WT     841  GTTAATTATTAAAGCTGACAGAAAGGTAATTTGTCCACTGTCTTACATAGCCTATATATA  900
            ||||||||||||||||||||||||||||||||||||||||||||    ||||||||||||||
Mut    901  GTTAATTATTAAAGCTGACAGAAAGGTAATTTGTCCACTGTCGCGTATAGCCTATATATA  960
```

CREB5

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WT     601  AAATGTCAAGGAGATAACCCTTGAGAAGATTCttttttttttttAAGTACACGTGAGCAT  659
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Mut    659  AAATGTCAAGGAGATAACCCTTGAGAAGATTCTTTTTTTTTTTTTAAGTACACTGTGGCAT  717
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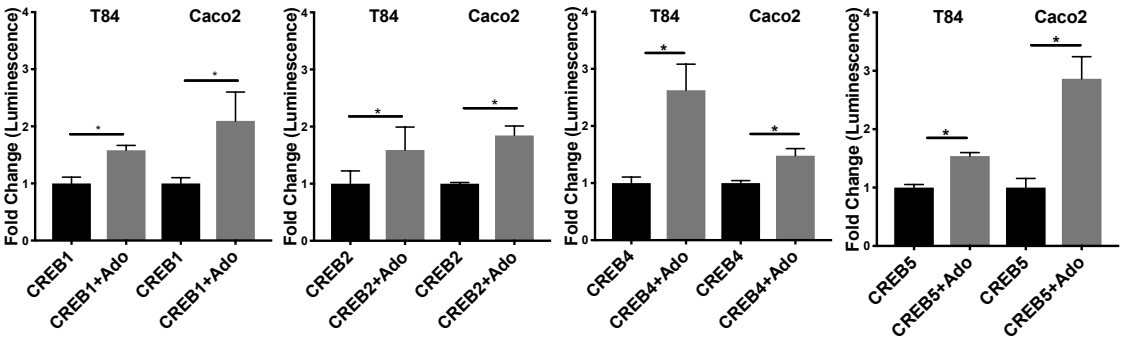
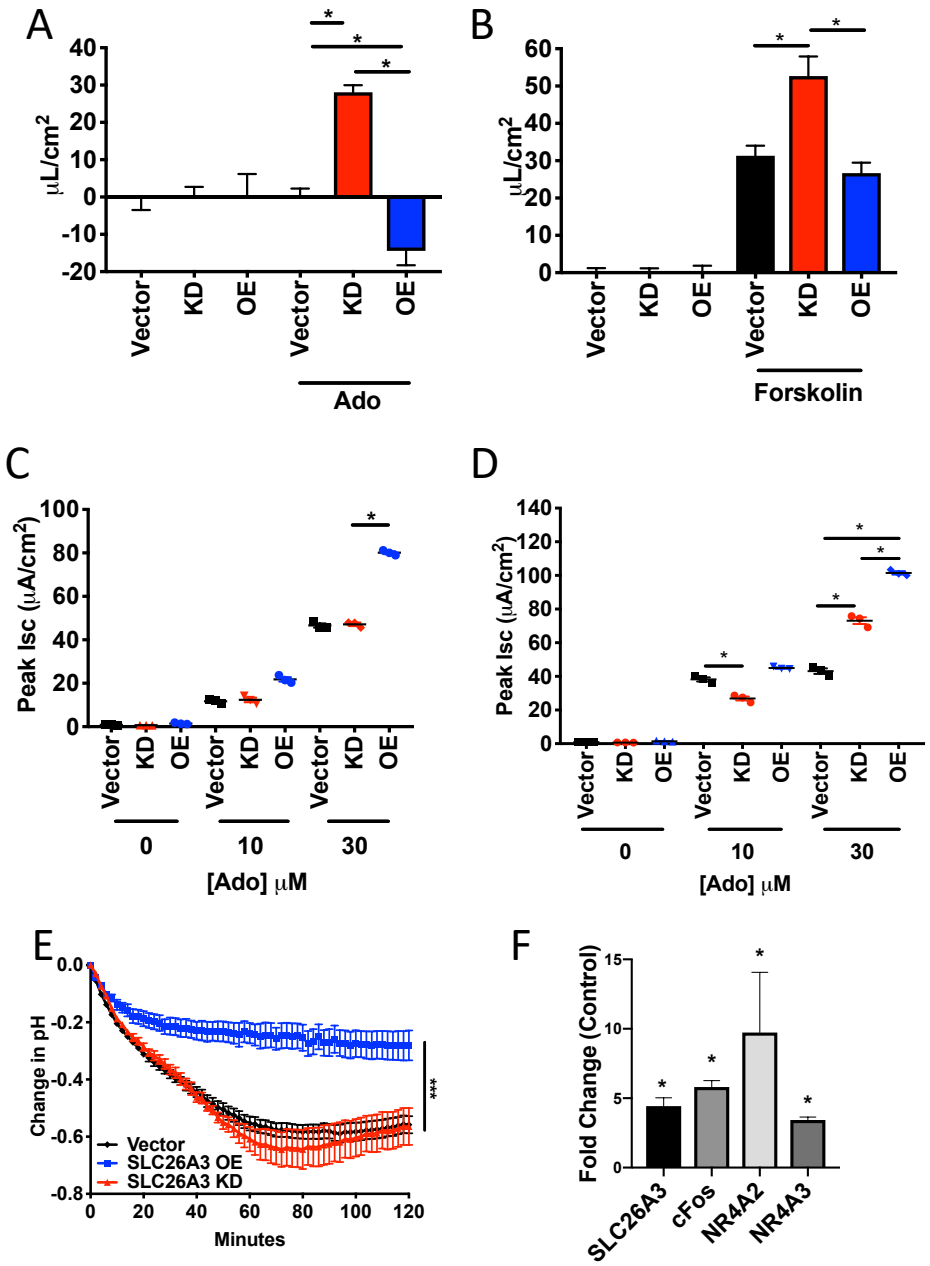
C

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μL/cm²
Vector
KD
OE
Ado
B
Forskolin
C
Peak Isc (μA/cm²)
[Ado] μM
D
E
Change in pH
Minutes
Vector
SLC26A3 OE
SLC26A3 KD
F
Fold Change (Control)
SLC26A3
cFos
NR4A2
NR4A3