Putative role of AMPK in fetal adaptive brain shut-down: linking metabolism and inflammation in the brain

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In a companion article of the same Research Topic, we present findings on the relationship of fetal adaptive brain shut-down and neuroinflammation during hypoxic acidemia (1). The findings are derived from the chronically instrumented non-anesthetized near-term ovine fetus model with and without chronic hypoxia (defined as arterial O₂Sat < 55%) subjected to umbilical cord occlusions (UCOs) of increasing severity. This model mimics human labor and is useful for studying the process of worsening acidemia that may precipitate perinatal brain injury. While the neuroinflammation overall decreases between 24 and 48 h post UCOs, the relationship between the degree of neuroinflammation and the timing of the adaptive brain shut-down reverses between these two time points, raising the question as to the underlying physiology.

We propose that adaptive brain shut-down in the fetus, evidenced by changes in EEG, may be mediated via adenosine monophosphate kinase (AMPK) signaling due to its controlling influence over cellular metabolism and interaction with inflammatory signaling pathways. By way of background, consider that the intracellular energy-sensor AMPK plays a key role in cellular metabolism, increases in cellular AMP/ATP ratio result in activation of AMPK via its phosphorylation, i.e., activation of the more energy-consuming NREM sleep state, which is associated with increased EEG delta wave activity and ATP increase in adult rats (4). Fetal adaptive neuronal shut-down with worsening acidemia may also be mediated via adenosine A₁ receptors (1, 5, 6). Notably, a combination of both A₁ and AMPK signaling is also a plausible mechanism leading to adaptive brain shut-down. First, Gadalla et al. observed that 5-aminoimidazole-4-carboxamide riboside (AICA riboside), a compound with neuroprotective properties thanks to the AMPK activation, has an additional neuroprotective effect under metabolic stress via competition with adenosine for uptake by the nucleoside transporter leading to an increase of extracellular adenosine and subsequent activation of A₁ receptors (7). Second, endogenous extracellular adenosine in physiological concentrations is, in turn, equally able to activate AMPK, an effect requiring active nucleoside transporters, such as CNT2 (8, 9). Both AMPK and A₁ receptor activation result in suppression of the more energy-consuming glutamatergic excitatory synaptic neurotransmission (i.e., as opposed to GABAergic inhibitory signaling contributing only ~20% to the neuronal oxidative energy metabolism) (10, 11). Either way, the result would be a relative increase of intracellular ATP and decreasing AMPK levels.

Sag et al. demonstrated in vitro that AMPK signaling and pro-inflammatory mediators in macrophages are mutually coupled via negative feedback. AMPK suppresses pro-inflammatory responses such as lipopolysaccharide (LPS)-induced production of TNF-α and IL-6 and promotes macrophage polarization to an anti-inflammatory functional phenotype with increased production of IL-10 (12). Exposure of macrophages to pro-inflammatory cytokines increases AMPK dephosphorylation, while exposure to anti-inflammatory cytokines results in rapid AMPK phosphorylation, i.e., activation (12). Activation of toll-like receptor (TLR) 4 on macrophages by LPS and resultant NF-κB pathway activation lead to a loss of AMPK phosphorylation (13). Hence, the effects of AMPK on the regulation of inflammatory status indicate that the presence of AMPK and its activation are important to counteract inflammation. Similarly, in vivo AMPK is down-regulated in all immune cells during experimental autoimmune encephalomyelitis (EAE), the animal model of the autoimmune disease multiple sclerosis (14). Neuronal AMPK is widely expressed in the embryonic and adult rat brains in situ and promotes neuronal survival under conditions of hypoglycemia in vitro (15).

Adenosine monophosphate kinase activity and its anti-inflammatory consequences have been studied in the context of chronic hypoxia. Chronic hypoxia up-regulates pAMPK in vitro in healthy neonatal rat neuronal slice cultures, in the human glioblastoma cells and in vivo in the adult rats’ pulmonary vasculature (7, 16, 17). Lactate is a principal energy source for neurons, especially in the developing brain (11, 18, 19). However, excess lactate within the extracellular space of the brain contributes to neuronal injury (3, 19). Recently, AMPK was also shown to play an important role in controlling the degree of
cellular inflammation in various cell types including glial cells, thus linking cellular metabolism and inflammation (2, 3, 20). Brain regional lactate acidosis increases neuronal intracellular pAMPK levels (21). At the same time, pAMPK also restricts AMPK induction follows within 5 days, as opposed to rats (22). 3 days old rat pups, and demonstrated on NF-κB metabolism and inflammation (2, 3, 20). including glial cells, thus linking cellular mechanisms in the perinatal brain, it seems plausible that lactic acidosis has the potential to induce variable degrees of microglial activation and neuronal shut-down in an AMPK-dependent manner, in chronically hypoxic fetuses with worsening acidemia. Further investigations are needed into the potential of intrapartum EEG–FHR monitoring to aid detection of adaptive brain shut-down to improve early postnatal diagnostic and therapeutic strategies, such as selecting at-risk newborns for hypothermic interventions to decrease cerebral metabolism (6, 23).

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REFERENCES

1. Xu A, Duroseri L, Ross MG, Hammond R, Richardson BS, Frasch MG. Adaptive brain shut-down counteracts neuroinflammation in the near-term ovine fetus. Front Neurosci (2014) 8:110. doi:10.3389/fneur.2014.00110
2. Meares GP, Qin H, Liu Y, Holdbrooks AT, Benveniste EN. AMP-activated protein kinase restricts IFN-γ-signaling, J Immunol (2013) 190:372–80. doi:10.4049/jimmunol.1202390
3. Nam HG, Kim W, Yoo DY, Choi JH, Won MH, Hwang JK, et al. Chronological changes and effects of AMP-activated kinase in the hippocampal CA1 region after transient forebrain ischemia in gerbils. Neuril Res (2013) 35:395–405. doi:10.1179/174312213Y.0000000158
4. Dvorak M, Mccarley BW, Kim T, Kalinchuk AV, Basheer R. Sleep and brain energy levels: ATP changes during sleep. J Neurosci (2010) 30:9007–16. doi:10.1523/JNEUROSCI.1423-10.2010
5. Hunter CJ, Bennett L, Power GG, Roelfsema RS, De Meester C, et al. Loss of AMPK exacerbates experimental autoimmune encephalomyelitis disease severity. Biochem Biophys Res Commun (2009) 386:16–20. doi:10.1016/j.bbrc.2009.05.106
6. Calimese M, Moonen J, Kemp BE, Mattson MP. AMP-activated protein kinase is highly expressed in neurons in the developing rat brain and promotes neuronal survival following glucose deprivation. J Mol Neurosci (2011) 47:16–26. doi:10.1007/s12031-010-9409-7
7. Wang X, Fan R, Lu Y, Yu C, Xu X, Zhang X, et al. Regulatory effect of AMP-activated protein kinase on pulmonary hypertension induced by chronic hypoxia in rats: in vivo and vitro studies. Mol Biol Rep (2014) 41(6):4031–41. doi:10.1007/s12033-014-3272-9
8. Abi-Saab WM, Maggs DG, Jones T, Jacob R, Srihari V, Thompson J, et al. Striking differences in glucose and lactate levels between brain extracellular fluid and plasma in conscious human subjects: effects of hyperglycemia and hypoglycemia. J Cereb Blood Flow Metab (2002) 22:271–9. doi:10.1097/00004467-200203000-00004
9. Prins ML. Cerebral metabolic adaptation and ketone metabolism after brain injury. J Cereb Blood Flow Metab (2008) 28(1):1–16. doi:10.1038/jcbfm.9060534
10. Xu A, Durosier L, Ross MG, Hammond R, Richardson BS, Frasch MG. Adaptive brain shut-down counteracts neuroinflammation in the near-term ovine fetus. Front Neurosci (2014) 8:110. doi:10.3389/fneur.2014.00110
11. Meares GP, Qin H, Liu Y, Holdbrooks AT, Benveniste EN. AMP-activated protein kinase restricts IFN-γ-signaling, J Immunol (2013) 190:372–80. doi:10.4049/jimmunol.1202390
12. Nam HG, Kim W, Yoo DY, Choi JH, Won MH, Hwang JK, et al. Chronological changes and effects of AMP-activated kinase in the hippocampal CA1 region after transient forebrain ischemia in gerbils. Neuril Res (2013) 35:395–405. doi:10.1179/174312213Y.0000000158
13. Dvorak M, Mccarley BW, Kim T, Kalinchuk AV, Basheer R. Sleep and brain energy levels: ATP changes during sleep. J Neurosci (2010) 30:9007–16. doi:10.1523/JNEUROSCI.1423-10.2010
14. Hunter CJ, Bennett L, Power GG, Roelfsema RS, De Meester C, et al. Loss of AMPK exacerbates experimental autoimmune encephalomyelitis disease severity. Biochem Biophys Res Commun (2009) 386:16–20. doi:10.1016/j.bbrc.2009.05.106
15. Calimese M, Moonen J, Kemp BE, Mattson MP. AMP-activated protein kinase is highly expressed in neurons in the developing rat brain and promotes neuronal survival following glucose deprivation. J Mol Neurosci (2011) 47:16–26. doi:10.1007/s12031-010-9409-7
16. Wang X, Fan R, Lu Y, Yu C, Xu X, Zhang X, et al. Regulatory effect of AMP-activated protein kinase on pulmonary hypertension induced by chronic hypoxia in rats: in vivo and in vitro studies. Mol Biol Rep (2014) 41(6):4031–41. doi:10.1007/s12033-014-3272-9
17. Abi-Saab WM, Maggs DG, Jones T, Jacob R, Srihari V, Thompson J, et al. Striking differences in glucose and lactate levels between brain extracellular fluid and plasma in conscious human subjects: effects of hyperglycemia and hypoglycemia. J Cereb Blood Flow Metab (2002) 22:271–9. doi:10.1097/00004467-200203000-00004
18. Prins ML. Cerebral metabolic adaptation and ketone metabolism after brain injury. J Cereb Blood Flow Metab (2008) 28(1):1–16. doi:10.1038/jcbfm.9060534
19. Pastor-Anglada M. Extracellular adenosine activates AMP-dependent protein kinase (AMPK). J Cell Sci (2006) 119:1612–21. doi:10.1242/jcs.02865
20. Rose JB, Cox IR. Physiology of nucleoside trans-: back to the future. Physiolog (Bethesda) (2008) 23:41–8. doi:10.1523/jphysiol.2006.0037
21. Patel AB, De Graaf RA, Mason GE, Rothman DL, Shulman RG, Bihari KL. The contribution of GABA to glutamate/glutamine cycling and energy metabolism in the rat cortex in vivo. Proc Natl Acad Sci U S A (2005) 102:5588–93. doi:10.1073/pnas.0501703102
22. Maniga S, Giove F, Tkac I, Logothetis NK, Henry PG, Olman CA, et al. Metabolic and hemodynamic events after changes in neuronal activity: current hypotheses, theoretical predictions and in vivo NMR experimental findings. J Cereb Blood Flow Metab (2009) 29:41–63. doi:10.1038/jcbfm.2008.134
23. Sug D, Carling D, Stout RD, Sattler J. Adeno- sine 5′-monophosphate-activated protein kinase promotes macrophage polarization to an anti-inflammatory functional phenotype. J Immunol (2008) 181:8633–41. doi:10.4049/jimmunol.181.12.8633
24. Violette B, Hornam S, Leclerc J, Lantier L, Foretz M, Billaud M, et al. AMPK inhibition in health and disease. Crit Rev Biochem Mol Biol (2010) 45:276–95. doi:10.3109/10409238.2010.482215
25. Nath N, Khan M, Rattan R, Mangalam A, Makkar RS, De Meester C, et al. Loss of AMPK exacerbates experimental autoimmune encephalomyelitis disease severity. Biochem Biophys Res Commun (2009) 386:16–20. doi:10.1016/j.bbrc.2009.05.106
26. Calimese M, Moonen J, Kemp BE, Mattson MP. AMP-activated protein kinase is highly expressed in neurons in the developing rat brain and promotes neuronal survival following glucose deprivation. J Mol Neurosci (2011) 47:15–45. doi:10.1007/s12031-014-1745-9
27. Neurath KM, Keouh MP, Mikkelsen T, Claffey KP. AMP-dependent protein kinase alpha 2 iso-
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20. Katerelos M, Mudge SJ, Stapleton D, Auwardt RB, Fraser SA, Chen CG, et al. 5-Aminoimidazole-4-carboxamide ribonucleoside and AMP-activated protein kinase inhibit signalling through NF-kappaB. *Immunol Cell Biol* (2010) 88:754–60. doi: 10.1038/icb.2010.44

21. Jiang P, Gan M, Ebrahim AS, Castanedes-Casey M, Dickson DW, Yen SH. Adenosine monophosphate-activated protein kinase overactivation leads to accumulation of alpha-synuclein oligomers and decrease of neurites. *Neurobiol Aging* (2013) 34:1504–15. doi: 10.1016/j.neurobiolaging.2012.11.001

22. Giri S, Nath N, Smith B, Viollet B, Singh AK, Singh I. 5-Aminoimidazole-4-carboxamide-1-beta-4-ribofuranoside inhibits proinflammatory response in glial cells: a possible role of AMP-activated protein kinase. *J Neurosci* (2004) 24:479–87. doi: 10.1523/JNEUROSCI.4288-03.2004

23. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* (2013) 1:CD003311. doi: 10.1002/14651858.CD003311.pub3

Conflict of Interest Statement: Martin G. Frasch is an inventor of the related patent application entitled “EEG Monitor of Fetal Health” including U.S. Patent Application Serial No. 12/532,874 and CA 2681926 National Stage Entries of PCT/CA08/00580 filed March 28, 2008, with priority to US provisional patent application 60/908,587, filed March 28, 2007. No other disclosures have been made.

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