Acetoacetate

The ketone bodies, especially the beta-Hydroxybutyric acid, had been shown to modulate the function of the central nervous system and prevent the pathological progression of Alzheimer's disease (AD). However, little is known about the role of acetoacetate in the AD brain. Thus, Wu et al. intraventricularly injected acetoacetate into familial AD mice (APPSWE) for 14 days and monitored their memory and biochemical changes. During the behavior test, acetoacetate at 100 mg/kg led to significant improvement in both Y-maze and novel object recognition tests (NORTs) (both $P < .05$), indicating ameliorating spatial and recognition memory, respectively. Biomedical tests revealed two mechanisms were involved. Firstly, acetoacetate inhibited the GPR43-pERK pathway, which led to apparent inhibition in tumor necrosis factor-α and Interleukin-6 expression in the hippocampus in a concentration-dependent manner. Secondarily, acetoacetate stimulated the expression of hippocampal brain-derived neurotrophic factor (BDNF). They concluded that acetoacetate could ameliorate AD symptoms and exhibited promising features as a therapeutic for AD [1)].

Pending classification

2: Schreck KC, Hsu FC, Berrington A, Henry-Barron B, Vizthum D, Blair L, Kossoff EH, Easter L, Whitlow CT, Barker PB, Cervenka MC, Blakeley JO, Strowd RE. Feasibility and Biological Activity of a Ketogenic/Intermittent-Fasting Diet in Patients With Glioma. Neurology. 2021 Aug 31;97(9):e953-e963. doi: 10.1212/WNL.0000000000012386. Epub 2021 Jul 7. PMID: 34233941; PMCID: PMC8589278.

3: Wenger KJ, Wagner M, Harter PN, Franz K, Bojunga J, Fokas E, Imhoff D, Rödel C, Rieger J, Hattingen E, Steinbach JP, Pilatus U, Voss M. Maintenance of Energy Homeostasis during Calorically Restricted Ketogenic Diet and Fasting-MR- Spectroscopic Insights from the ERGO2 Trial. Cancers (Basel). 2020 Nov 27;12(12):3549. doi: 10.3390/cancers12123549. PMID: 33261052; PMCID: PMC7760797.

4: Vallejo FA, Shah SS, de Cordoba N, Walters WM, Prince J, Khatib Z, Komotar RJ, Vanni S, Graham RM. The contribution of ketone bodies to glycolytic inhibition for the treatment of adult and pediatric glioblastoma. J Neurooncol. 2020 Apr;147(2):317-326. doi: 10.1007/s11060-020-03431-w. Epub 2020 Feb 24. PMID: 32096068.

5: Schoeler NE, Bell G, Yuen A, Kapelner AD, Heales SJR, Cross JH, Sisodiya S. An examination of biochemical parameters and their association with response to ketogenic dietary therapies. Epilepsia. 2017 May;58(5):893-900. doi: 10.1111/epi.13729. Epub 2017 Apr 3. PMID: 28369834.

6: Tamaki T, Node Y, Teramoto A. Changes of the plasma ketone body level and arterial ketone body ratio at the onset of mild aneurysmal subarachnoid hemorrhage. Neurol Res. 2008 Nov;30(9):898-902. doi: 10.1179/016164108×323708. Epub 2008 Aug 7. PMID: 18691448.

7: Tamaki T, Shibata Y, Node Y, Yamamoto Y, Teramoto A. [Metabolic acidosis and ketone body in severely head-injured patients]. No Shinkei Geka. 2000 Jul;28(7):623-9. Japanese. PMID: 10920824.

8: Nishiyama T, Yokoyama T, Hanaoka K. Effects of sevoflurane and isoflurane anesthesia on arterial ketone body ratio and liver function. Acta Anaesthesiol Scand. 1999 Mar;43(3):347-51. doi: 10.1034/j.1399-6576.1999.430318.x. PMID: 10081544.

9: Tamaki T, Isayama K, Shibata Y, Kimura A, Yamamoto Y, Teramoto A. [Changes of arterial ketone

body ratio (AKBR) in patients with intracerebral hemorrhage]. No Shinkei Geka. 1998 Jul;26(7):591-7. Japanese. PMID: 9666492.

10: Tamaki T, Isayama K, Teramoto A. [Changes in arterial ketone body ratio (AKBR) in subarachnoid hemorrhage patients]. No To Shinkei. 1996 Feb;48(2):161-7. Japanese. PMID: 8865696.

11: Robertson CS, Goodman JC, Narayan RK, Contant CF, Grossman RG. The effect of glucose administration on carbohydrate metabolism after head injury. J Neurosurg. 1991 Jan;74(1):43-50. doi: 10.3171/jns.1991.74.1.0043. PMID: 1984505.

12: Hong JY, Ning SM, Ma BL, Lee MJ, Pan JM, Yang CS. Roles of pituitary hormones in the regulation of hepatic cytochrome P450IIE1 in rats and mice. Arch Biochem Biophys. 1990 Aug 15;281(1):132-8. doi: 10.1016/0003-9861(90)90422-u. PMID: 2116767.

13: Go KG, Prenen GH, Paans AM, Vaalburg W, Kamman RL, Korf J. Positron emission tomography study of 11C-acetoacetate uptake in a freezing lesion in cat brain, as correlated with 11C-tyrosine and 18F-fluorodeoxyglucose uptake, and with proton magnetic resonance imaging. Adv Neurol. 1990;52:525-8. PMID: 2396544.

14: Prenen GH, Go KG, Zuiderveen F, Paans AM, Vaalburg W. An improved synthesis of carbon-11 labeled acetoacetic acid and an evaluation of its potential for the investigation of cerebral pathology by positron emission tomography. Int J Rad Appl Instrum A. 1990;41(12):1209-16. doi: 10.1016/0883-2889(90)90208-x. PMID: 1963420.

15: Prenen GH, Go KG, Paans AM, Zuiderveen F, Vaalburg W, Kamman RL, Molenaar WM, Zijlstra S, Elsinga PH, Sebens JB, et al. Positron emission tomographical studies of 1-11C-acetoacetate, 2-18F-fluoro-deoxy-D-glucose, and L-1-11C-tyrosine uptake by cat brain with an experimental lesion. Acta Neurochir (Wien). 1989;99(3-4):166-72. doi: 10.1007/BF01402328. PMID: 2788974.

16: Go KG, Prenen GH, Korf J. Protective effect of fasting upon cerebral hypoxic-ischemic injury. Metab Brain Dis. 1988 Dec;3(4):257-63. doi: 10.1007/BF00999535. PMID: 3241603.

17: Robertson CS, Clifton GL, Grossman RG, Ou CN, Goodman JC, Borum P, Bejot S, Barrodale P. Alterations in cerebral availability of metabolic substrates after severe head injury. J Trauma. 1988 Nov;28(11):1523-32. doi: 10.1097/00005373-198811000-00002. PMID: 3184214.

18: Clejan S, Schulz H. Effect of growth hormone on fatty acid oxidation: growth hormone increases the activity of 2,4-dienoyl-CoA reductase in mitochondria. Arch Biochem Biophys. 1986 May 1;246(2):820-8. doi: 10.1016/0003-9861(86)90338-3. PMID: 3707134.

19: Lying-Tunell U, Lindblad BS, Malmlund HO, Persson B. Cerebral blood flow and metabolic rate of oxygen, glucose, lactate, pyruvate, ketone bodies and amino acids. Acta Neurol Scand. 1981 Jun;63(6):337-50. doi: 10.1111/j.1600-0404.1981.tb00788.x. PMID: 7324866.

20: Woods HF, Graham CW, Green AR, Youdim MB, Grahame-Smith DG, Hughes JT. Some histological and metabolic properties of an isolated perfused rat brain preparation with special reference to monoamine metabolism. Neuroscience. 1976 Aug;1(4):313-23. doi: 10.1016/0306-4522(76)90058-0. PMID: 11370515.

21: Fredholm BB, Linde B, Persson B. Effects of fasting on adipose tissue perfused in situ in young dogs. Scand J Clin Lab Invest. 1973 Jan;31(1):79-86. doi: 10.3109/00365517309082421. PMID: 4687779.

22: Lin CH, Fritz IB. Studies on spermatogenesis in rats. IV. Rates of oxidation of palmitate and pyruvate by various testicular cell populations. Can J Biochem. 1972 Sep;50(9):963-8. doi: 10.1139/o72-133. PMID: 5073274.

23: Newsholme EA, Randle PJ. Regulation of glucose uptake by muscle. 7. Effects of fatty acids, ketone bodies and pyruvate, and of alloxan-diabetes, starvation, hypophysectomy and adrenalectomy, on the concentrations of hexose phosphates, nucleotides and inorganic phosphate in perfused rat heart. Biochem J. 1964 Dec;93(3):641-51. doi: 10.1042/bj0930641. PMID: 4220951; PMCID: PMC1214023.

1)

Wu XJ, Shu QQ, Wang B, Dong L, Hao B. Acetoacetate Improves Memory in Alzheimer's Mice via Promoting Brain-Derived Neurotrophic Factor and Inhibiting Inflammation. Am J Alzheimers Dis Other Demen. 2022 Jan-Dec;37:15333175221124949. doi: 10.1177/15333175221124949. PMID: 36113018.