# D-allose

D-allose is a rare naturally occurring monosaccharide, which is a simple sugar. It is an aldohexose, meaning it has six carbon atoms and an aldehyde functional group. Alloses are a type of sugar that are epimers of aldohexoses—specifically, they differ in the stereochemistry at the C-3 carbon atom.

D-allose is a stereoisomer of D-glucose, and they differ in the configuration of the hydroxyl group at the third carbon atom. In D-allose, the hydroxyl group on the third carbon is in the D configuration, whereas in D-glucose, it is in the L configuration. The “D” designation indicates the stereochemistry of the highest numbered chiral carbon in the molecule.

D-allose is not as common as some other sugars like glucose or fructose, but it can be found in small amounts in certain natural sources. It has been studied for its potential health benefits and properties. As with other monosaccharides, it can be involved in various biological processes and can serve as a source of energy for living organisms.

---

Ischemic stroke (IS) occurs when a blood vessel supplying the brain becomes obstructed, resulting in cerebral ischemia. This type of stroke accounts for approximately 87% of all strokes. Globally, IS leads to high - mortality and poor prognosis and is associated with neuroinflammation and neuronal apoptosis. D-allose is a bio-substrate of glucose that is widely expressed in many plants.

---

A previous study showed that D-allose exerted neuroprotective effects against acute cerebral ischemia-reperfusion injury by reducing neuroinflammation. Luo et al. aimed to clarify the beneficial effects D-allose in suppressing IS-induced neuroinflammation damage, cytotoxicity, neuronal apoptosis and neurological deficits and the underlying mechanism in vitro and in vivo.

In vivo, an I/R model was induced by middle cerebral artery occlusion and reperfusion (MCAO/R) in C57BL/6 N mice, and D-allose was given by intraperitoneal injection within 5 min after reperfusion. In vitro, mouse hippocampal neuronal cells (HT-22) with oxygen-glucose deprivation and reperfusion (OGD/R) were established as a cell model of IS. Neurological scores, some cytokines, cytotoxicity and apoptosis in the brain and cell lines were measured. Moreover, Gal-3 short hairpin RNAs, lentiviruses and adeno-associated viruses were used to modulate Gal-3 expression in neurons in vitro and in vivo to reveal the molecular mechanism.

D-allose alleviated cytotoxicity, including cell viability, LDH release and apoptosis, in HT-22 cells after OGD/R, which also alleviated brain injury, as indicated by lesion volume, brain edema, neuronal apoptosis, and neurological functional deficits, in a mouse model of I/R. Moreover, D-allose decreased the release of inflammatory factors, such as IL-1β, IL-6 and TNF-α. Furthermore, the expression of Gal-3 was increased by I/R in wild-type mice and HT-22 cells, and this factor further bound to TLR4, as confirmed by three-dimensional structure prediction and Co-IP. Silencing the Gal-3 gene with shRNAs decreased the activation of TLR4 signaling and alleviated IS-induced neuroinflammation, apoptosis and brain injury. Importantly, the loss of Gal-3 enhanced the D-allose-mediated protection against I/R-induced HT-22 cell injury, inflammatory insults and apoptosis, whereas activation of TLR4 by the selective agonist LPS increased the degree of neuronal injury and abolished the protective effects of D-allose.

In summary, D-allose plays a crucial role in inhibiting inflammation after IS by suppressing Gal-3/TLR4/PI3K/AKT signaling pathway in vitro and in vivo [1)].

---

Cell viability of RBMECs was suppressed after hypoxia/reoxygenation (H/R) treatment and significantly increased after d-allose supplementation. RNAseq results showed 180 differentially expressed genes (DEGs) between the therapy group (H/R + Dal) and the model group (H/R), of which 151 DEGs were restored to control levels by d-allose. Enrichment analysis revealed that DEGs were mainly involved in protein processing in endoplasmic reticulum. 6 DEGs in the unfolded protein response (UPR) pathway were verified by qRT-PCR. All of them were significantly down-regulated by d-allose, indicating that endoplasmic reticulum stress (ERS) was relieved. In addition, d-allose significantly inhibited the phosphorylation level of eIF2α, a marker of ERS. The downstream molecules of Phosphorylation of eIF2α, Gadd45a and Chac1, which trigger cycle arrest and apoptosis, respectively, were also significantly inhibited by d-allose. Thus, we conclude that d-allose inhibits the UPR pathway, attenuates eIF2α phosphorylation and ERS, restores the cell cycle, inhibits apoptosis, and thus enhances endothelial cell tolerance to H/R injury [2)].

---

A study investigates the effects of d-allose, a rare sugar, on the inflammatory response after transient forebrain ischemia in the gerbil and whether it reduces oxidative stress (8-hydroxyl-2'-deoxyguanosine levels) and behavioral deficits.

Transient forebrain ischemia was induced by occlusion of the bilateral common carotid arteries for 5 minutes. d-Allose was intraperitoneally injected immediately after ischemia (400 mg/kg). Inflammatory cytokines and oxidative damage in the hippocampus and behavioral deficits were examined 3 days after ischemia.

d-Allose administration reduced ischemia-induced cytokine production, oxidative stress, and behavioral deficits (motor and memory related).

Conclusions: The present results suggest that d-allose reduces brain injury after transient global ischemia by suppressing inflammation as well as by inhibiting oxidative stress [3)]

---

Early experiments confirmed that D-allose was closely involved in the blood brain barrier (BBB) protection from ischemia reperfusion (IR) injury, but the regulatory mechanism is not fully defined. In this study, we aimed to investigate the role of D-allose in the protection of BBB integrity and the relevant mechanisms involved in the mice model of middle cerebral artery occlusion and reperfusion (MCAO/Rep). D-allose was intravenously injected via a tail vein (0.2mg/g and 0.4mg/g, 1h before ischemia), GW9662 was intraperitoneal injected to the mice (4mg/kg) before inducing ischemia 24h. Pretreatment with D-allose ameliorated the neurological deficits, infarct volume and brain edema in brains of MCAO/Rep mice. D-allose inhibited cell apoptosis in the mice model of MCAO/Rep. We observed that D-allose remarkably decreased BBB permeability and prevented the reduction of ZO-1, Occludin and Claudin-5 in mice brains with MCAO/Rep injury. D-allose also repressed the levels of TNF-α, NF-κB, interleukin (IL)-1β and IL-8 in inflammatory responses. The increases of intercellular adhesion molecular-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and CD11b/CD18 were significantly inhibited by D-allose during the MCAO/Rep injury. And D-allose decreased the L-selectin and P-selectin levels after MCAO/Rep. Moreover, D-allose induced up-regulation of peroxisome

proliferator-activated receptor γ (PPARγ), and down-regulation of TNF-α and NF-κB after MCAO/Rep, which were abolished by utilization of GW9662. In conclusion, we provided evidences that D-allose may has therapeutic potential against brain IR injury through attenuating BBB disruption and the inflammatory response via PPARγ-dependent regulation of NF-κB [4].

---

Transient forebrain ischemia was induced by occlusion of the bilateral common carotid arteries for 5 min. D-Allose was intravenously injected before and after ischemia (200 mg/kg). Extracellular glutamate and lactate release from the gerbil brain, and $PO_2$ profiles were monitored during ischemia and reperfusion. We also examined neuronal death and oxidative damage in the hippocampus one week after ischemia reperfusion, and investigated functional outcome. D-Allose administration suppressed glutamate and lactate release compared to vehicle controls. Brain damage, 8-OHdG levels (a marker of oxidative stress) and locomotor activities were significantly decreased by D-allose treatment. The present results suggest that d-allose reduces delayed neuronal death and behavioral deficits after transient ischemia by changing cerebral metabolism and inhibiting oxidative stress [5].

1)
Luo Y, Cheng J, Fu Y, Zhang M, Gou M, Li J, Li X, Bai J, Zhou Y, Zhang L, Gao D. D-allose Inhibits TLR4/PI3K/AKT Signaling to Attenuate Neuroinflammation and Neuronal Apoptosis by Inhibiting Gal-3 Following Ischemic Stroke. Biol Proced Online. 2023 Nov 28;25(1):30. doi: 10.1186/s12575-023-00224-z. PMID: 38017376.
2)
Zhang M, Fu YH, Luo YW, Gou MR, Zhang L, Fei Z, Gao DK. d-allose protects brain microvascular endothelial cells from hypoxic/reoxygenated injury by inhibiting endoplasmic reticulum stress. Neurosci Lett. 2023 Jan 10;793:137000. doi: 10.1016/j.neulet.2022.137000. Epub 2022 Dec 5. PMID: 36473686.
3)
Shinohara N, Nakamura T, Abe Y, Hifumi T, Kawakita K, Shinomiya A, Tamiya T, Tokuda M, Keep RF, Yamamoto T, Kuroda Y. d-Allose Attenuates Overexpression of Inflammatory Cytokines after Cerebral Ischemia/Reperfusion Injury in Gerbil. J Stroke Cerebrovasc Dis. 2016 Sep;25(9):2184-8. doi: 10.1016/j.jstrokecerebrovasdis.2016.01.030. Epub 2016 Jun 21. PMID: 27342700.
4)
Huang T, Gao D, Hei Y, Zhang X, Chen X, Fei Z. D-allose protects the blood brain barrier through PPARγ-mediated anti-inflammatory pathway in the mice model of ischemia reperfusion injury. Brain Res. 2016 Jul 1;1642:478-486. doi: 10.1016/j.brainres.2016.04.038. Epub 2016 Apr 19. PMID: 27103568.
5)
Liu Y, Nakamura T, Toyoshima T, Shinomiya A, Tamiya T, Tokuda M, Keep RF, Itano T. The effects of D-allose on transient ischemic neuronal death and analysis of its mechanism. Brain Res Bull. 2014 Oct;109:127-31. doi: 10.1016/j.brainresbull.2014.10.005. Epub 2014 Oct 14. PMID: 25445611.