NEUROBIOGEN

Introduction

NEUROBIOGEN prioritizes its research and development efforts to develop innovative new medicine to treat patients who suffer from degenerative brain diseases and central nervous system diseases.

By developing innovative drugs through the efficacy verification and clinical progress of our new drug candidates (KDS2010/Tisolagiline), we will continue our journey to a global company to contribute to human health after all.

Mission & Vision

- Innovative new medicine R&D company treating degenerative brain diseases and central nervous system diseases

KDS2010 (Tisolagiline) is a reversible inhibitor derived from a new treatment mechanism for Alzheimer's, and we're developing a new drug based on the mechanism of KDS2010 that improves cognitive function by acting on reactive astrocytes.

- Global bio-company at home and abroad

Our vision is to grow into a global leading company that is respected worldwide, not just in Korea.

- Innovative company, the bridge head for conquering human diseases and moving toward a better future

Our vision is to play a key role in finding a way to the future in which incurable diseases that at present mankind has not overcome can finally be cured.

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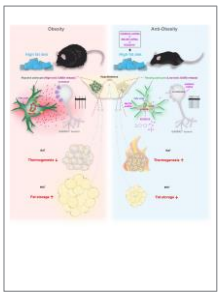
Pipeline

			In-vitro In-vivo	IP (Korea)	IP (Global)	Publication
As Is	1	Alzheimer's disease	Complete	Registered	USA, Canada, Australia, Japan, Russia, [1] EU(8Countries), China, India Registered	Nature Medicine(2014.06) Science Advance(2019.03) Nature Neurosci (2020.12)
	2	Post stroke	Complete	Registered	Japan, Russia, China Registered	Cell Reports(2020.07)
	3	Spinal cord injury	Complete	Registered	Japan, Russia, Australia, China, Canada Registered	Cell (Under Revision)
	4	Obesity	Complete	Registered	USA, Canada, Australia, Japan, Russia, [1] EU(8Countries), China, India, Registered	Nature Metabolism (in press)
	5	Parkinson's disease	Complete	Registered	USA, Canada, Australia, Japan, Russia, [1] EU(8Countries), China, India, Registered	Neurotherapeutics(2021.10)
To-be	6	Multiple sclerosis	On-going			
	7	Post Traumatic Stress Disorder	On-going			

[1] EU(8 Countries) : France, UK, Germany Swiss, Spain, Italy, Portugal, Belgium

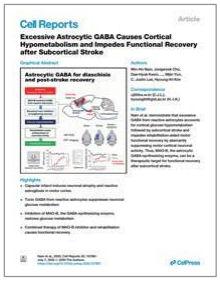
Publications



- Nature Metabolism

Reactive astrocytes in Lateral Hypothalamic Area causes MAOB-dependent GABA production and obesity

2023. 08.31.



- Cell Reports

Excessive Astrocytic GABA Causes Cortical Hypometabolism and Impedes Functional Recovery after Subcortical Stroke

2020. 7. 7.

- Science Advances

Newly developed reversible MAO-B inhibitor circumvents the shortcomings of irreversible inhibitors in Alzheimer's Disease

2019. 3. 20.

- Nature Medicine

GABA from reactive astrocytes impairs memory in mouse models of Alzheimer's Disease

2014. 6. 29.

CEO
SangWook KIM

swkneurobiogen@daum.net
+82-10-7504-0914 / +82-70-4018-8008
+82-2-3486-2613

www.neurobiogen.com/eng
2F Bangbae building, 9, Myeongdal-ro, Seocho-gu, Seoul, Korea

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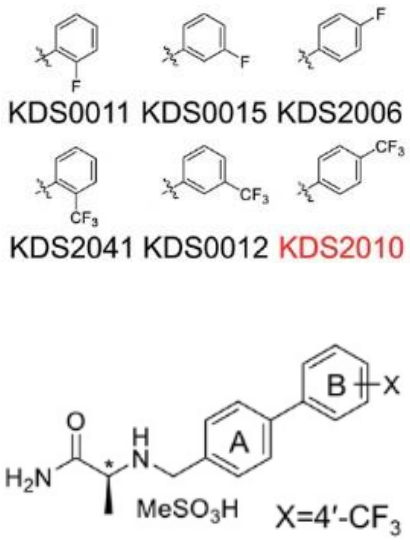
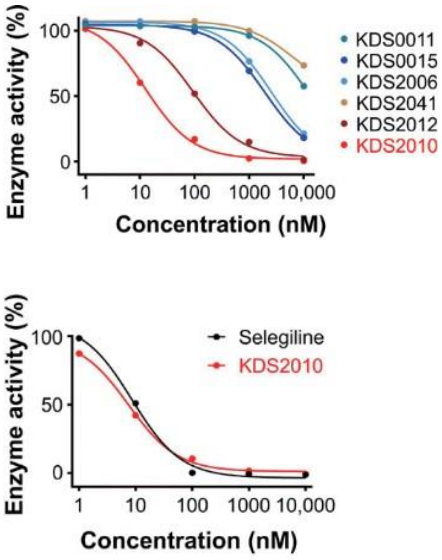
KDS2010

Selective Reversible MAO-B Inhibitor Alzheimer's Disease

▶ KDS2010(Tisolagiline) is a new, potent, selective, and reversible MAO-B inhibitor.



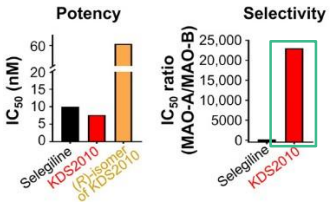
Chemical structure of KDS2010 and selected derivatives



Concentration-enzyme activity curves for Selegiline(irreversible) and KDS2010 in the MAO-B enzyme assay (n = 4 assays)

Potent & Selective Inhibitor, KDS2010 is the best-in-class MAO-B inhibitor.

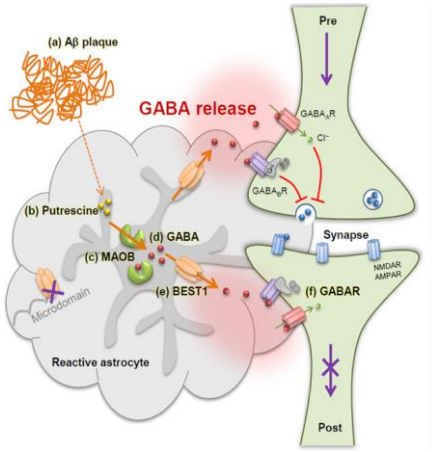
Compound	hMAO-B (IC_{50})	hMAO-A (IC_{50})	Selectivity (MAO-A/MAO-B)	
KDS2010	7.6 nM	> 100 μM	> 10000	Reversible, very selective
Safinamide	79 nM	> 80 μM	> 1013	Reversiblr, but multi-target
RG-1577	15 nM (6 nM*)	3.85* μM	~ 653	Reversible, not selective
Selegiline	10 nM (9 nM*)	1.5 μM*	~ 150	Irreversible, not selective
rasagiline	14 nM*	710 nM*	~ 50	Irreversible, not selective



Potency and selectivity of selegiline and KDS2010 based on IC_{50} (in nM) levels of MAO-B and the isoform MAO-A.

▶ Mechanism of Astrocyte & GABA in AD.

MAO-B as a potential therapeutic target for treating memory impairments in AD.



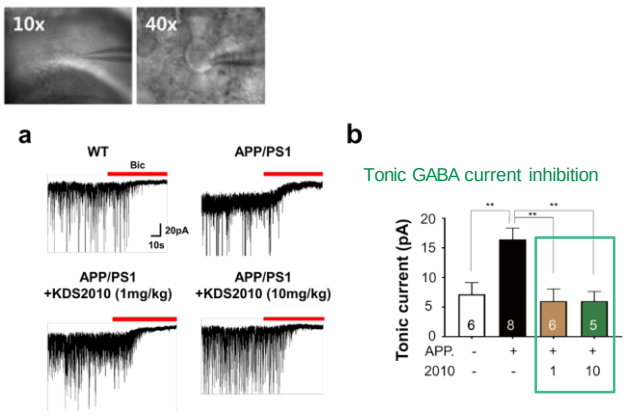
Alzheimer's disease

- a Reactive astrocytes clusters around Aβ plaques
- b Putrescine concentration ↑ in reactive astrocytes
- c GABA synthesized from Putrescine through MAO-B
- d Increased GABA is released from reactive astrocytes through Best1 channel
- e Released GABA binds extrasynaptic GABA receptors

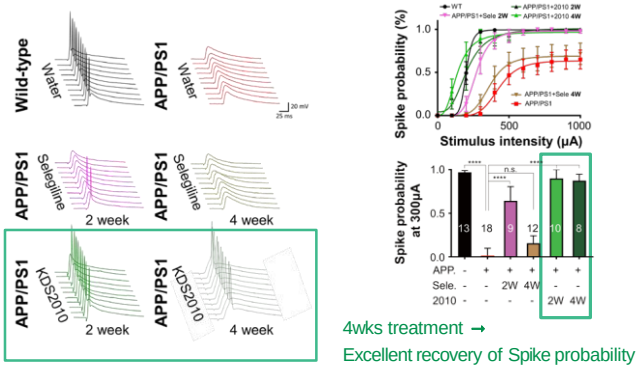
Learning and memory impairment

▶ KDS2010 is effective in both short-term and long-term treatments.

KDS2010 significantly decreased tonic GABA current in APP/PS1



KDS2010's recovery of spike probability in APP/PS1 mouse model



4wks treatment →
Excellent recovery of Spike probability

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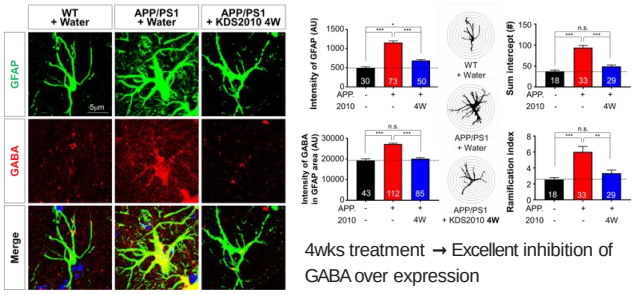
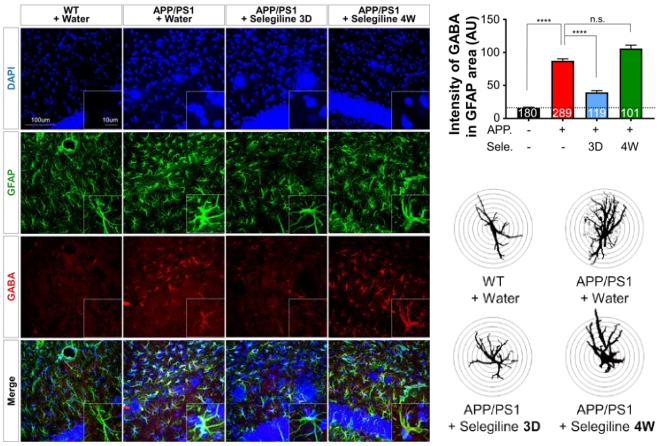
▶ KDS2010(Tisolagiline) is effective in both short-term and long-term treatments.

KDS2010 significantly decreased tonic GABA production in vs Selegiline (Irreversible inhibitor) APP/PS1 (Long-term treatment)



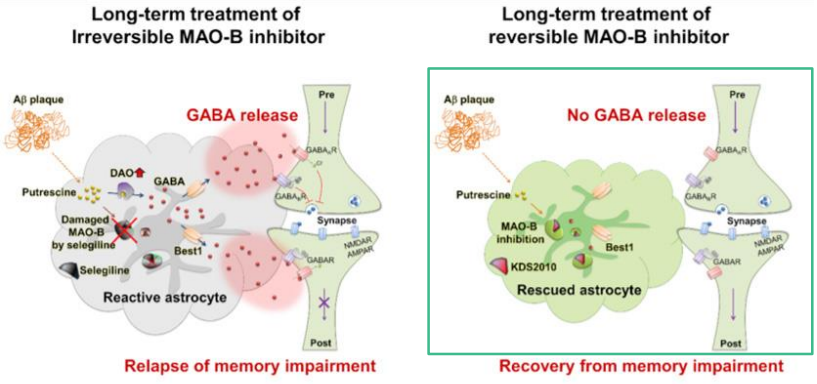
4wks treatment → Excellent inhibition of GABA over expression



▶ Advantage of reversible MAO-B inhibitor.

DAO is the main compensatory GABA-synthesizing enzyme in long-term selegiline treatment.

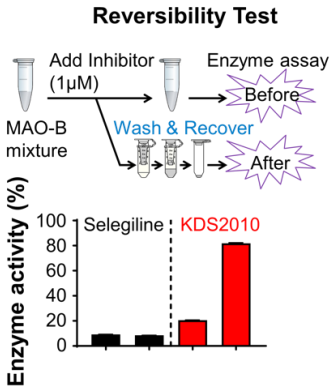
In contrast, long-term treatment with KDS2010 (Tisolagiline) persistently blocked the aberrant tonic GABA current in APP/PS1 mice.



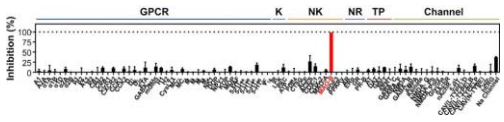
Longterm treatment with KDS2010 (Tisolagiline) does not induce compensatory mechanisms.

Fig. S9. Model diagrams of long-term treatment of AD with either irreversible or reversible MAO-B inhibitors. Aβ: amyloid-beta, MAO-B: monoamine oxidase-B, DAO: diamine oxidase, Best1: bestrophin 1, Pre: presynaptic terminal, Post: postsynapse, NMDAR: *N*-methy-*D*-aspartate receptor, AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor

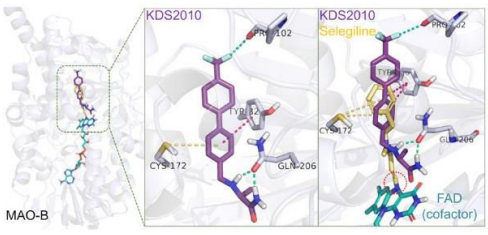
▶ KDS2010(Tisolagiline) is a new, potent, selective, and reversible MAO-B inhibitor.



We observed that KDS2010 caused an over 80% recovery of enzyme activity, whereas almost no recovery was observed for Selegiline.



We observed an outstanding off-target selectivity at 1 μM KDS2010 (no other target causing >40% inhibition).



We found that KDS2010 was a competitive inhibitor, targeting the same binding cavity as selegiline, but its interaction with critical residues in the MAO-B binding cavity was more compact and reversible.

CEO
SangWook KIM

swkneurobiogen@daum.net
+82-10-7504-0914 / +82-70-4018-8008
+82-2-3486-2613

www.neurobiogen.com/eng
2F Bangbae building, 9, Myeongdal-ro, Seocho-gu, Seoul, Korea

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KDS2010

Selective Reversible MAO-B Inhibitor Obesity

nature metabolism

Article

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Hypothalamic GABRA5-positive neurons control obesity via astrocytic GABA

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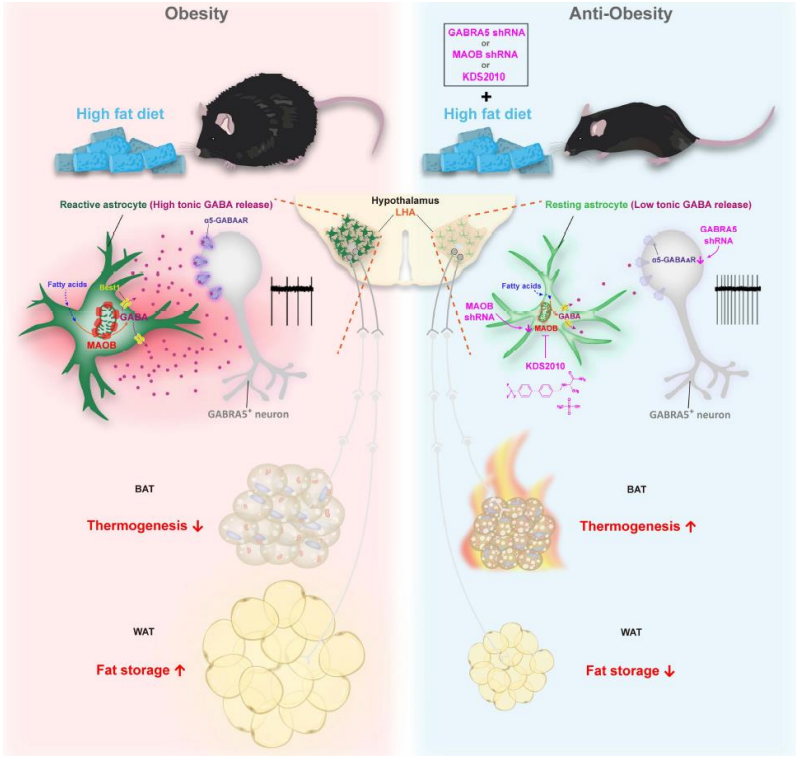
Moonsun Sa[1,2], Eun-Seon Yoo[3], Wuhyun Koh[1], Mingu Gordon Park[1], Hyun-Jun Jang[4], Yong Ryoul Yang[4], Mridula Bhalla[1,5], Jae-Hun Lee[1], Jiwoon Lim[1,5], Woojin Won[1], Jea Kwon[1], Joon-Ho Kwon[1], Yejin Seong[1], Byungeun Kim[6,7], Heeyoung An[3], Seung Eun Lee[6], Kl Duk Park[4,7], Pann-Ghill Suh[4], Jong-Woo Sohn[3] & C. Justin Lee[1,2]

The lateral hypothalamic area (LHA) regulates food intake and energy balance. Although LHA neurons innervate adipose tissues, the identity of neurons that regulate fat is undefined. Here we show that GABRA5-positive neurons in LHA ($GABRA5^{LHA}$) polysynaptically project to brown and white adipose tissues in the periphery. $GABRA5^{LHA}$ are a distinct subpopulation of GABAergic neurons and show decreased pacemaker firing in diet-induced obesity mouse models in males. Chemogenetic inhibition of $GABRA5^{LHA}$ suppresses fat thermogenesis and increases weight gain, whereas gene silencing of GABRA5 in LHA decreases weight gain. In the diet-induced obesity mouse model, $GABRA5^{LHA}$ are tonically inhibited by nearby reactive astrocytes releasing GABA, which is synthesized by monoamine oxidase B (Maob). Gene silencing of astrocytic Maob in LHA facilitates fat thermogenesis and reduces weight gain significantly without affecting food intake, which is recapitulated by administration of a Maob inhibitor, KDS2010. We propose that firing of $GABRA5^{LHA}$ suppresses fat accumulation and selective inhibition of astrocytic GABA is a molecular target for treating obesity.

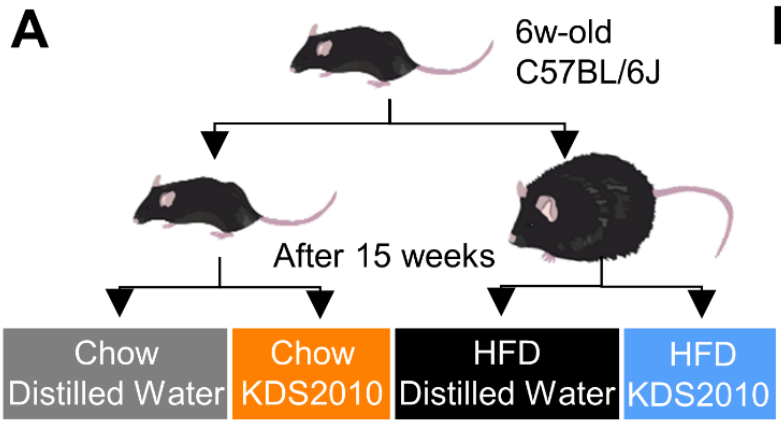
Individuals with obesity have an imbalance in food intake and energy expenditure (EE), both of which are regulated by neural circuits that work inside the hypothalamus and extend beyond the hypothalamus[1,2]. The hypothalamus consists of a number of small nuclei, which include the lateral hypothalamic area (LHA). Although LHA occupies an extended field of the hypothalamus, it is substantially less anatomically defined[3–5]. A subpopulation of LHA neurons are known to innervate brown adipose tissue (BAT) and white adipose tissue (WAT) to mediate thermogenesis in BAT, browning of WAT and energy storage in WAT[3,6]. However, the precise cell types that innervate BAT and WAT to mediate thermogenesis and energy storage are still under active investigation.

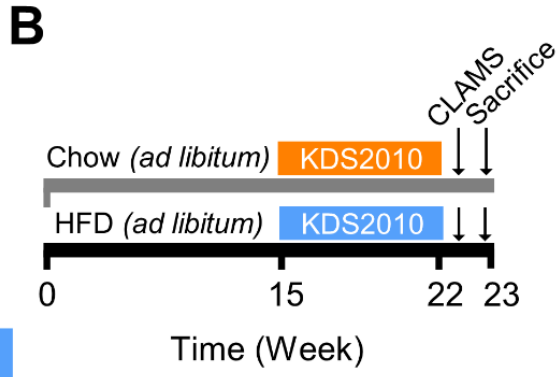
The LHA contains several cell types expressing different transmitters and hormones, including neurons expressing melanin-concentrating hormone (MCH) and hypocretin/orexin[7–10]. MCH neurons in LHA negatively regulate BAT activity to suppress EE[11], whereas orexin neurons send excitatory projections to increase BAT activity and EE with decreasing in food intake[11,12]. In addition, LHA contains other neurons that express neither MCH nor orexin[9–10]. A large population of GABAergic neurons in LHA are intrinsically depolarized and distinct from MCH and orexin[10]. These GABAergic neurons are defined by the presence of components necessary for GABA synthesis and release, including GAD65, GAD67 and vesicular GABA transporter[13–15]. Due to their location in LHA,

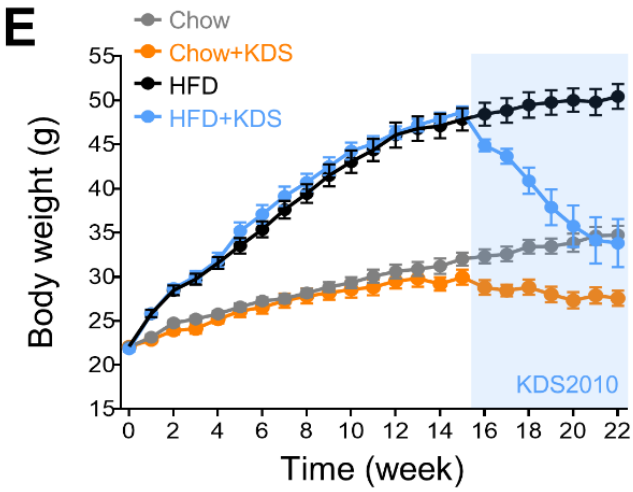
[1]Center for Cognition and Sociality, Institute for Basic Science, Daejeon, Republic of Korea. [2]KU-KIST Graduate School of Converging Science and Technology, Korea University, Seongbuk-gu, Seoul, Republic of Korea. [3]Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Daejeon, Republic of Korea. [4]Ulsan National Institute of Science and Technology, Ulsan, Republic of Korea. [5]IBS School, University of Science and Technology, Daejeon, Republic of Korea. [6]Center for Brain Disorders, Brain Science Institute, Korea Institute of Science and Technology, Seoul, Republic of Korea. [7]Division of Bio-Medical Science and Technology, University of Science and Technology, Daejeon, Republic of Korea. [8]Virus Facility, Research Animal Resource Center, Korea Institute of Science and Technology, Seoul, Republic of Korea. e-mail: cjl@ibs.re.kr

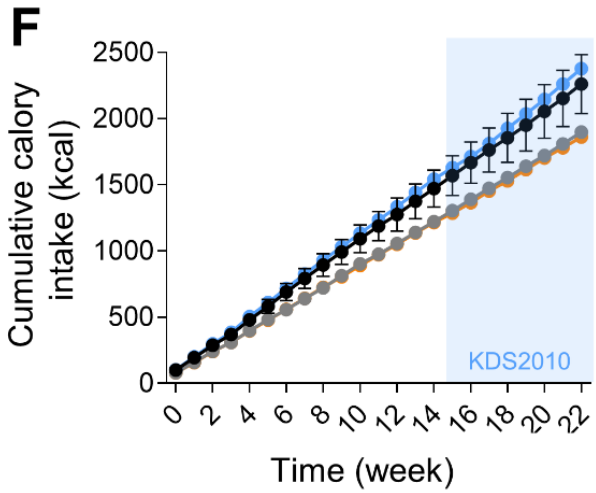


KDS2010 effectively and rapidly reduces obesity









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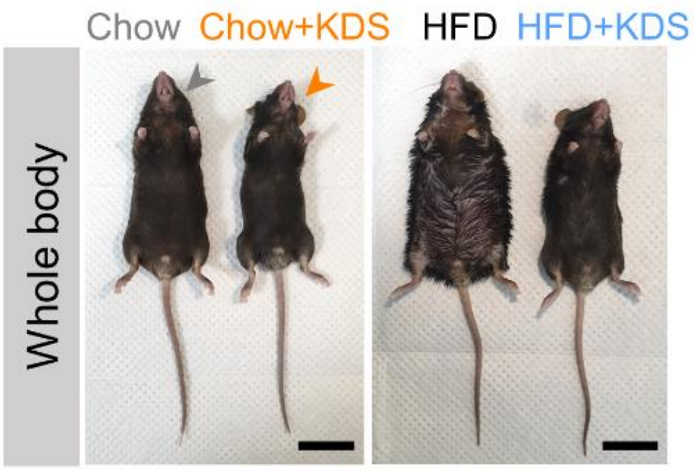
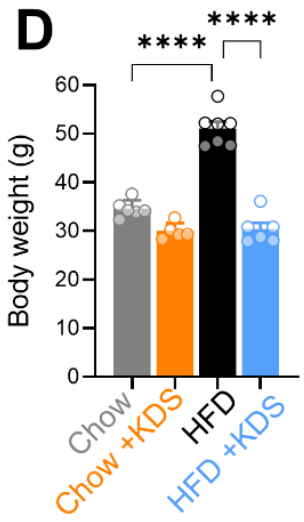
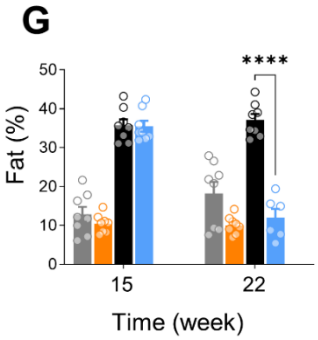
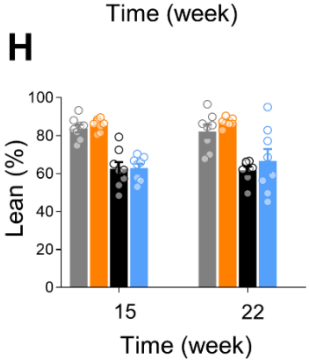
KDS2010 effectively and rapidly reduces obesity

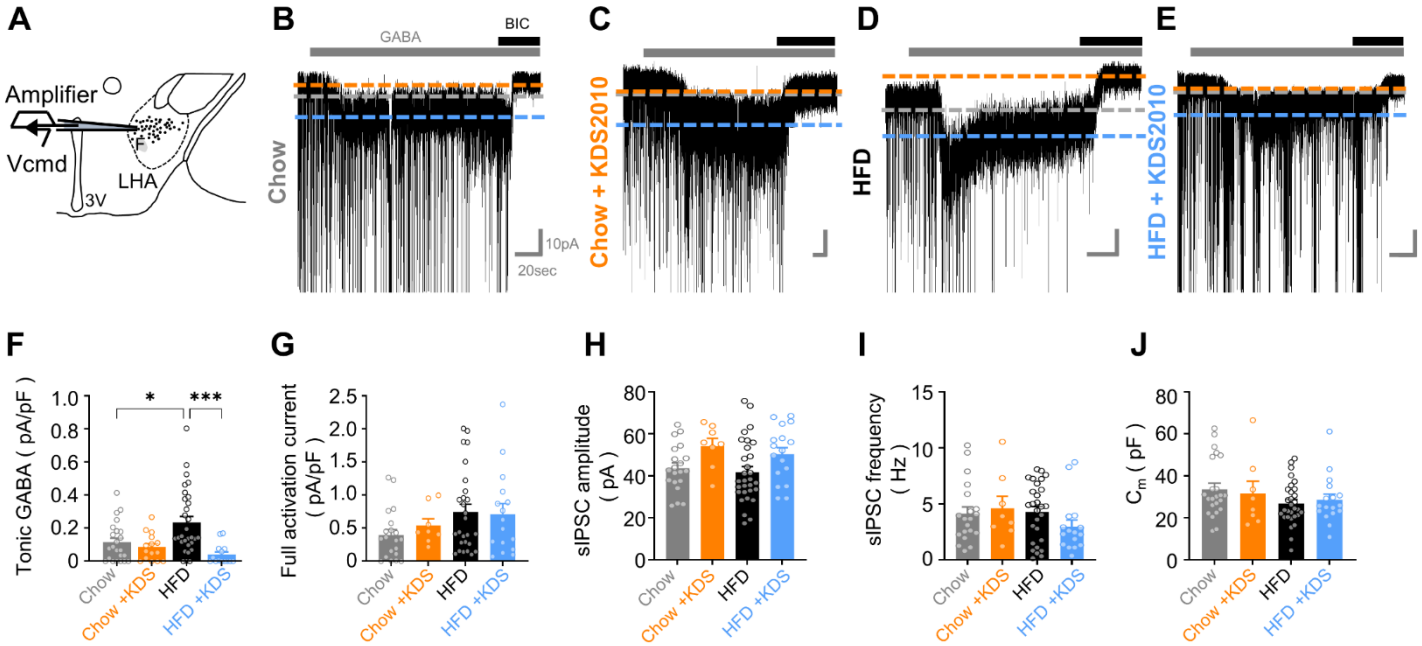


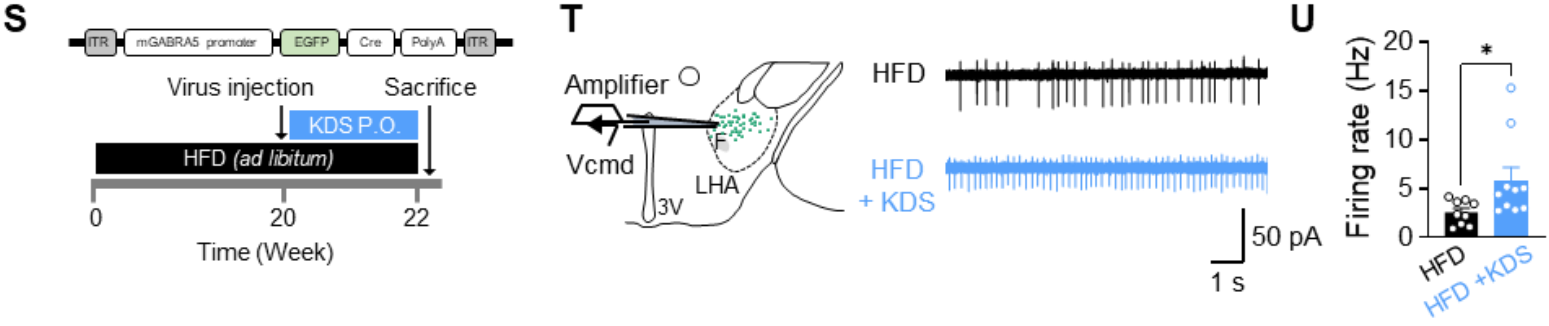






KDS2010 attenuates the elevated tonic inhibition in LHA





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SangWook KIM

swkneurobiogen@daum.net
+82-10-7504-0914 / +82-70-4018-8008
+82-2-3486-2613

www.neurobiogen.com/eng
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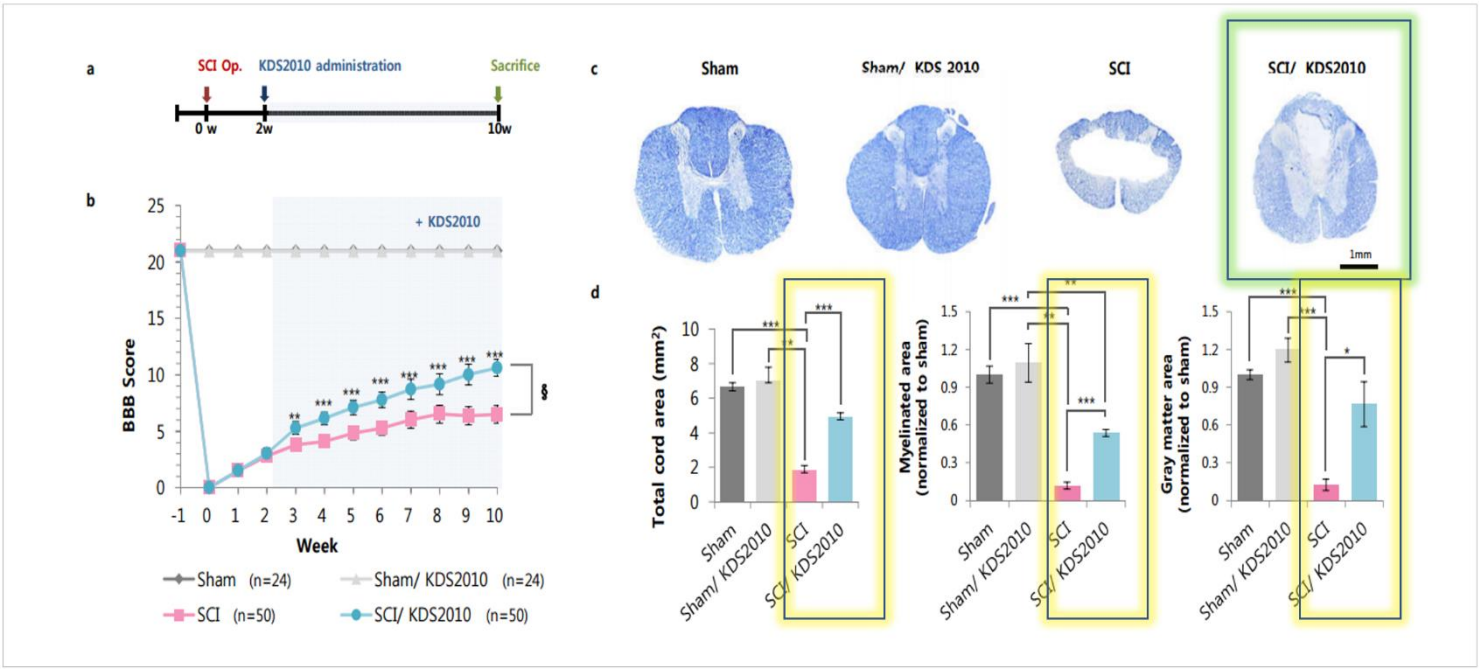
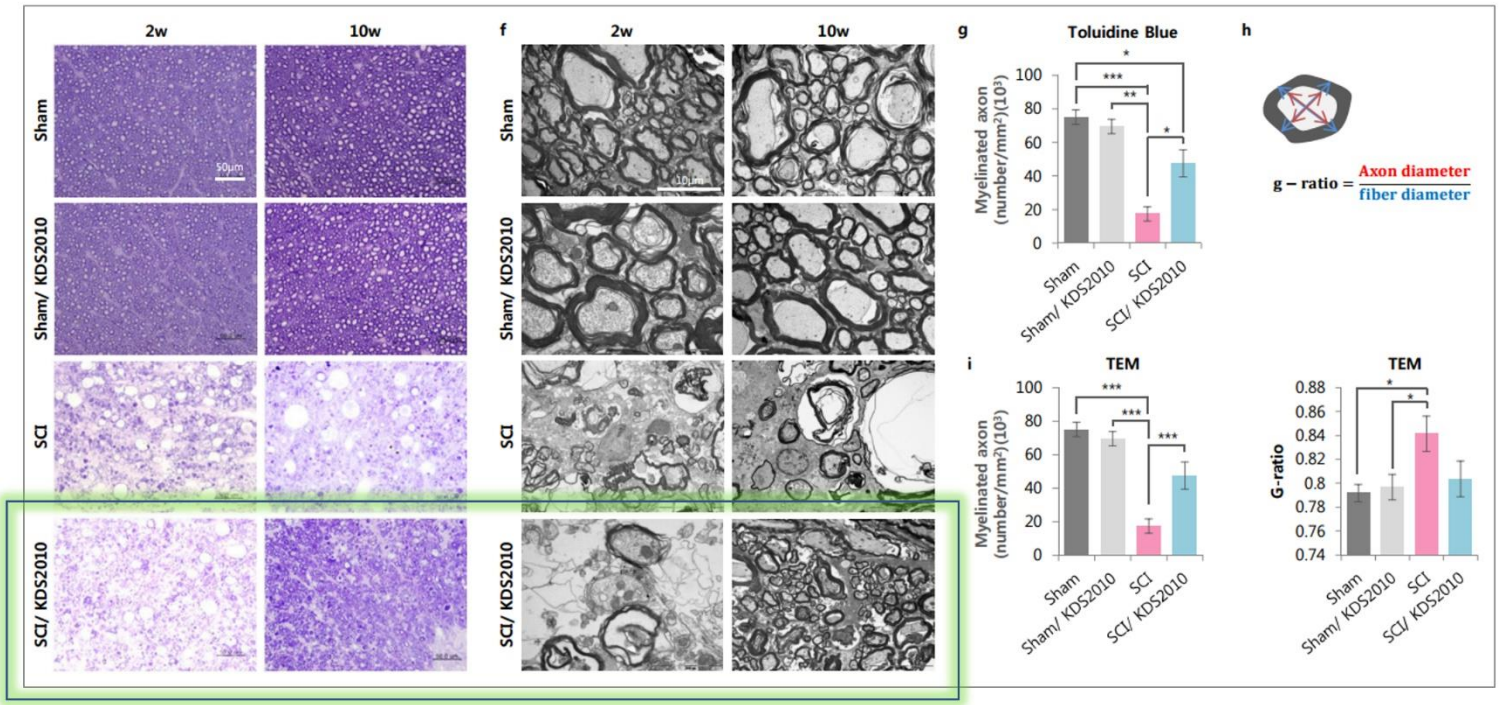
KDS2010

Selective Reversible MAO-B Inhibitor Spinal Cord Injury

KDS2010 causes motor recovery, remyelination, and neuronal regeneration.





CEO
SangWook KIM

swkneurobiogen@daum.net
+82-10-7504-0914 / +82-70-4018-8008
+82-2-3486-2613

www.neurobiogen.com/eng
2F Bangbae building, 9, Myeongdal-ro, Seocho-gu, Seoul, Korea