significance in various disease and conditions [77]. It is sulfur analog of water, and because of its weak intermolecular force, it exists in gaseous form [78]. It is synthesized via both enzymatic and non-enzymatic pathways inside mammalian tissue, but non-enzymatic route accounts for a small portion. Cystathionine β-synthase (CBS) and Cystathionine γ-lyase (CSE) are two enzymes responsible for biosynthesis of H_2S from L-cysteine [79, 80]. 3-mercaptopyruvate sulfurtransferase (3MST) is another enzyme that can generate H_2S through cys-catabolism pathway. CSE and CBS are localized in the cytoplasm of cell, but 3MST is expressed partly in mitochondria and cytoplasm [81, 82]. A recent study showed H_2S could be produced from D-cysteine via enzyme D-amino acid oxidase (DAO) [83, 84]. Non-enzymatically, it can be produced from thiosulfate [14] and glucose (via glycolysis) or from phosphogluconate via NADPH oxidase [85, 86]. Although H_2S has beneficial roles in various hematologic diseases, urological disease, cardiovascular functioning and oxidative stress, the effect of H_2S in CNS has attracted a lot of attention over the past few years [14, 77, 87]. Expression of different H_2S producing enzymes in various parts of mammalian tissues is listed in Table 3 [88]. Important signaling events of H_2S in various neuronal cells/cell lines are listed below [89]:

1. Inhibition of monoamine oxidase (via catecholamines)
2. NMDA potentiation (via glutamate)
3. Cystic fibrosis transmembrane conductance regulator (CTFR) channel activation (via chloride channels)
4. K_{ATP} and K_{Ca2+} channel activation (via potassium channels)
5. Intracellular calcium mobilisation, L-type and T-type channel activation (via calcium channels)
6. Supression of various types of neuronal toxicity (via oxidative stress)
7. Inhibition of p38-MAPK (via mitogen and tyrosine kinase receptors)
8. Stimulation of PKA and elevation of cAMP (via PKA)

AD, a common form of dementia, characterized by memory impairment, personality changes, and various neuropsychiatric symptoms which cause neuronal apoptosis, neuronal inflammation (induced by amyloid-β), and increased oxidative stress [90–93]. Level of H_2S in the brain of patient with AD is lower than healthy people of same age [94]. A recent study revealed that in a rat model of vascular dementia, plasma H_2S level was lower and i.p. injection of NaHS (H_2S donor) protected neuronal injury and improved behavioral (learning and memory) tests results [95]. Another study demonstrated that progression of AD was abrupted after treatment with spa-water rich of H_2S content [96]. Role of H_2S in the improvement of cognitive functioning, spatial learning and memory [96], and neuroprotective effects [14, 90, 93, 97] is also providing us hopes against the AD.

PD is characterized by progressive degeneration of dopaminergic neurons in the substantia nigra of midbrain which is age-related and leads to the formation of Lewy bodies in soma of residual neurons [77, 98]. Previous studies based on animal models found that inhalation or injection of H_2S donors prevented abnormalities related to PD (microglial activation or motor dysfunction) including neuroprotective, neuromodulatory, and therapeutic roles of H_2S in PD [99–101]. H_2S-mediated anti-oxidative, anti-inflammatory, anti-apoptotic, and pro-survival effects linked with PD is also reviewed in recent paper [102].

TBI is one of the most common causes of death among youth in today's world and is considered as a public health epidemic. Memory impairment and cognitive dysfunction are two immediate effects of TBI whereas rapid and extreme production of ROS are also associated with secondary neuronal injury after TBI [103–106]. Karimi et al. injected NaHS intraperitoneally and observed neuroprotective effect of H_2S in TBI induced impaired memory in rats [103]. Zhang et al. found H_2S as a neuromodulator by injecting same H_2S donor which decreased TBI induced lesion volume in brain [107]. NaHS proved to be the neuroprotective in various other pathological conditions [108–112]. These studies are also supported by recent finding which showed dynamic changes in CBS and H_2S levels in various part of the brain in experimental TBI models [107].

Huntington's Disease (HD) is associated with neurotoxicity, behavioural changes, impairment of motor coordination, and oxidative stress. Paul et al. showed that there is a reduction of level of CSE in mammalian tissues with HD. They demonstrated that loss of CSE mediates degeneration of neuronal cells and progression of HD [113, 114]. Studies have shown that patients with Down Syndrome (DS) has the higher level of CBS compared to that of a normal individual. This overexpression of CBS is believed to be the cause of abnormal cognitive ability in children with DS and may lead to AD in DS adults. Overproduction of H_2S is also associated with ethylmalonic encephalopathy [115]. Some other neuroprotective [40, 78, 116–118], neurotransmissive role (facilitation of the induction of hippocampal LTP)

Table 3 Expression of different H_2S producing enzymes in various parts of mammalian tissues

H_2S producing enzymes	Expression
CSE	Liver, Kidney, Aorta, Ileum but weakly found in brain.
CBS	Liver, Kidney, and Brain (astrocytes)
3MST	Liver, Kidney, Heart, Brain (Purkinje cells of cerebellum, pyramidal neurons of cerebellar cortex, hippocampus, mitral cells of olfactory bulb, retinal neurons), Vascular endothelium, Smooth muscle.