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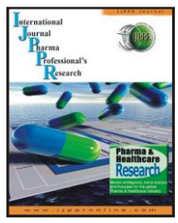
Review Article



MITOGEN ACTIVATED PROTEIN KINASE AT THE CROSSROADS OF ALZHEIMER'S DISEASES

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Abstract

Alzheimer's disease (AD) is associated with various neurodegenerative alterations and inflammation thought to play a major role in its pathogenesis. The Mammalian stress activated protein kinase (SAPK), p38 mitogen-activated protein kinases (MAPKs), a family of serine/threonine protein kinases, activated in response to wide range of cellular stresses as well as in response to inflammatory mediators. A large body of evidences indicates that p38MAPK activity is critical for normal immune and inflammatory response. Moreover, the p38 MAPK pathway is considered to be a key regulator of various inflammatory pathways which are activated during normal aging and AD therapy. The p38MAPK pathway which is a key regulator of pro-inflammatory cytokines biosynthesis at the transcriptional and translational levels, which makes different components of this pathway, a potential targets for the treatment of autoimmune and inflammatory diseases. Furthermore, p38 MAPK is over expressed in AD and have been linked to Aβ deposition and Tau tangle formation. Favourable modulator of p38 MAPK found to beneficial in a variety of experimental models of AD, further implicating p38 MAPK in AD pathogenesis. In this review, we provide an overview on p38 MAPK and its implication in the pathogenesis of Alzheimer's diseases.

Key words: - SB203580; p38 MAPK; Alzheimer's disease; ICV STZ; Memory; Oxidative stress.

Introduction

Alzheimer's diseases (AD) is an age related irreversible, progressive neurodegenerative disorder characterized by amyloid beta deposition and Tau tangle formation and inability to form new memories and access existing ones, due to neuronal cell death in the hippocampus and frontal cortex [1,2]. Extensive evidences suggests that oxidative stress and neuroinflammation are the earlier events in AD pathology [3,4]. Moreover, oxidative stress and neuroinflammatory events have been linked to Aβ deposition and Tau tangle formation [5]. Furthermore, during aging energy failure, oxidative stress and early increase in inflammatory mediators provides the basis for persistent stress to the neurons contributes to impaired synaptic functions, cognitive decline and neuronal death [6]. Although the neuropathological features of AD have been well defined, the underlying mechanisms responsible for the pathogenic processes have not been clearly delineated. This lack of understanding of the fundamental processes that are responsible for the neurodegeneration in AD likely is the reason there are no effective treatments to prevent the onset progression of the disease. However, research advances over the past several years have begun to provide some insight into the molecular mechanisms of AD. One particularly important area of investigation is the contribution of aberrant cell signaling events to the pathogenic process. For example, recent findings have provided strong evidence that the p38 mitogen activated protein (MAP) kinase signaling cascade is one signaling pathway that overactivated in AD. Advances in molecular biology have led us to understand the molecular mechanisms involved in mediating stress response and subsequent neuronal death. Recently, it has been reported that stress activated protein kinases plays a major role in degeneration of neurons in AD pathology. Mainly, two SAPK's such as JNK and p38 MAPK have been implicated in tau hyperphosphorylation, amyloid beta deposition and in progression of inflammation that are being actively involved in the pathogenesis of AD [7-10] and may be attractive targets for neurodegenerative diseases [11,12]. In this review, we mainly focused on p38 mitogen activated protein kinase (MAPK) pathway, a major proinflammatory signal transduction pathway activated by various extracellular stimulation such as growth factors, oxidative stress, ultraviolet and cytokines, are hyperactivated in human AD brain [13-15]. *In vitro* and *In vivo* studies have been demonstrated that upon activation, p38 MAPK cascade leading to cause neuronal death through various pathways in brain including, activation of microglia/astroglia in the production of inflammatory mediators such as IL-1β, TNF-α, increase expression of COX/LOX and iNOS [16,17]. Oxidative/nitrosative stress and excitotoxicity which also contribute to phosphorylate p38 MAPK [15,18,19]. However, extracellular accumulation of Aβ [7,8,10,20,21] and hyperphosphorylation of Tau protein [10,22-25] which are main hallmark of AD, are also activated via the phosphorylation of p38 MAPK in the hippocampal area of brain. Moreover, in Alzheimer's diseases, p38 MAPK also leads to desensitization of the insulin receptor [26,27] and degeneration of the cholinergic neurons, further leads to memory and cognitive dysfunction [20]. Neuronal apoptosis process also mediated by p38 MAPK [28]. Phosphorylated form of p38 MAPK also activate transcriptional factors such as MAPKAK2, PRAK, ATF-2, CHOP, NF-kB, AP-1, ATF-2 which further increases the expression of iNOS and many proinflammatory cytokines [29,30], all these changes are nearly relevant to the pathogenesis of AD brain via activation

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of p38 mitogen activated protein kinase and this hyperactivation of the p38 kinase and related signal pathway provides a new concept for discussing neuroinflammation in the aging human brain and may indicate a novel therapeutic target of the AD brain.

Overview Of Mitogen activated protein kinase (MAPK)

Cellular behavior in response to extracellular stimuli is mediated through intracellular signaling pathways such as the mitogen-activated protein (MAP) kinase pathways [31]. MAP kinases are members of discrete signaling cascades and serve as focal points in response to a variety of extracellular stimuli. Four distinct subgroups within the MAP kinase family have been described: **(1)** extracellular signal-regulated kinases (ERKs), **(2)** C-jun N-terminal or stress-activated protein kinases (JNK/SAPK), **(3)** ERK/ big MAP kinase-1 (BMK1), and **(4)** the p38 group of protein kinases. The focus of this review is to highlight the characteristics of the p38 kinases, components of this kinase cascade, activation of this pathway and the biological consequences of its activation [32].

Table 1: p38 MAPK nomenclature and localization

Name	Alternate name	localization
P38 α	Sapk2b, csbp1	Ubiquitously
p38β	Sapk2b, p38-2	Ubiquitously
p38 γ	Sapk3 erk6	Skeletal muscle
p38δ	Sapk4	Low in most tissues

Table 2: Extracellular stimulants for the activation of p38 MAPK

Growth factors	angiotensin ii, fgf, pdgf, vegf, tgf-β, igf
Cytokines	Tnf-α, il-1β, cd154, il-17
Stress factors	Lps, mechanical stress, uv radiation, osmotic stress
Others	Thrombin, high glucose, endothelin, no, estradiol, insulin, gpcr, tkr

Table 3: Enzymes and substrates for the activation and inactivation of p38 MAPK

Upstrem activator	Mapkkk (mkkk or mekk 1/4, raf, ask1, mlk3, tak1, tao-1/3) mapkk(mkk3/4/6, mek1/2)
Inactivation enjymes	Map (mitogen activated protein kinase phosphatase) Serine/threonine protein phosphatsse type 2c (pp2c)
Downstream substrate	Mapkap2/mk2, mk3, lsp1, creb, elf-4e, mnk1/2, Prak
Transcriptional factors	Atf-1/2/6, srf, sap1, chop, p53, c/ebpβ, mef2a/2c, mitf1, ddit3, elk1, nfat, hbp1, ap-1, nf-kb, stat1/3

p38 MAP Kinase

p38α (p38) was first isolated as a 38 kDa protein and is known to be rapidly tyrosine phosphorylated in response to LPS stimulation [33]. p38 cDNA was also cloned as a molecule that binds puridinyl imidazole derivatives which are known to inhibit biosynthesis of inflammatory cytokines such as interleukin-1 (IL-1) and tumor-necrosis factor (TNF) in LPS stimulated monocytes [34]. To date, four splice variants of the p38 family have been identified: p38α, p38β [35,36], p38γ [37,38], and p38δ (SAPK4) [39]. Of these, p38α and p38β are ubiquitously expressed while p38γ and p38δ are differentially expressed depending on tissue type. All p38 kinases can be categorised by a Thr-Gly-Tyr (TGY) dual phosphorylation motif [40]. Sequence comparisons have revealed that each p38 isoform shares~60% identity within the p38 group but only 40-45% to the other three MAP kinase family members [41].

Localization of p38 MAPK in Brain

Despite an abundance of data concerning p38 activation and function in peripheral tissues, the role of p38 in the brain is poorly understood. This is surprising while considering the fact that p38 is more highly expressed in brain than in peripheral tissues [35,39]. Only the p38α and p38β isoforms are expressed in the brain, with high levels of protein in most major brain regions, including cerebral cortex, hippocampus, cerebellum, and several brainstem nuclei [29]. Detected mainly in neurons, p38α is found in the nucleus, dendrites, and in cytoplasmic regions of the cell body. Both neurons and glia express p38β, with a pronounced nuclear location. The α and β isoforms of p38 are especially enriched in hippocampus, the brain region predominantly involved in learning and memory. Further, they are heavily expressed in pyramidal neurons of CA1 and CA3 regions of hippocampus as well as in granule cells of the dentate gyrus [29,42]. Unlike p38α, p38β is detected in glial cells of the CA1 region also. In addition to prominent mRNA and protein levels, p38 also exhibits a high basal activity in brain [29,43], which suggest that the p38 pathway may play a role in normal neuronal function in addition to its role as an SAPK. Unlike JNK, whose function(s) are preferentially related to the control of apoptosis, p38 in the brain is involved not only in apoptosis, but also in aspects of neuronal differentiation, synaptic function and neuronal plasticity. Additionally, the p38 pathway is active during the induction of

long-term depression (LTD), a form of plasticity that is the functional inverse of LTP [44](Pei et al., 2001) and is involved in associative learning [45-47]

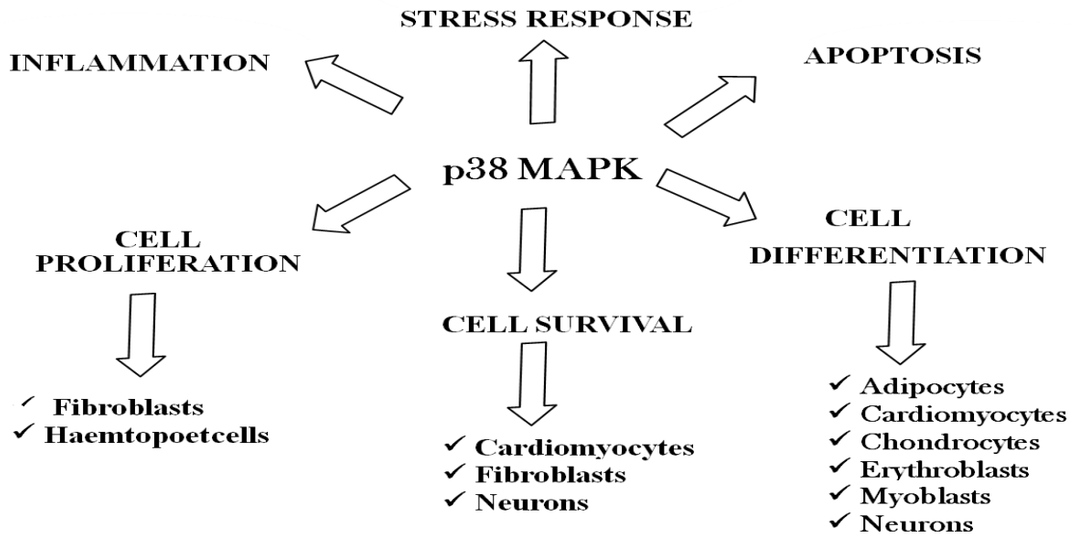

Fig-1 Biological functions of p38 MAPK

Implication Of P38 Mapk In Alzheimer's Diseases At Various States

p38 MAPK Activation In Tau Hyperphosphorylation

p38 has been demonstrated in vitro to phosphorylate tau on residues known to be phosphorylated in NFTs extracted from AD brains [25,48-50]. However, many other kinases, such as glycogen synthase kinase (GSK)-3β and extracellular signal-regulated kinase (ERK)-2, have also been implicated as tau kinases, with different kinases demonstrating different preferences for certain sites [50]. Many of these kinases, including p38, have been demonstrated to phosphorylate tau when co-transfected with tau into cells, with GSK-3 β demonstrating the best activity [51,52]. Although encouraging, the extrapolation of these data to AD is limited by caveats around overexpression and the use of non-neuronal cells. Therefore, current knowledge does not indicate the best target for intervention in tau phosphorylation in vivo, and further elucidation in this area is required. Additionally, it is not known if inhibition of any single kinase will have an impact on NFT formation. Although p38 has been implicated in tau phosphorylation in vitro and is associated in activated form with NFTs in AD in situ, there is currently no evidence that p38 phosphorylates tau in vivo. The activation of p38 has been demonstrated concurrently in conjunction with tau phosphorylation in the brains of rats implanted with IL-1-impregnated pellets; however, these results remain correlative [13,53]. Recently, p38 activation has been demonstrated in a murine amyloidogenic model of AD in which mutated APP is overexpressed, and activation correlated with plaque burden and tau phosphorylation in the brains of these mice [8]. Assessing a p38 inhibitor in such a model may elucidate the role of p38 in tau phosphorylation and plaque formation in vivo. However, it is important to keep in mind that although these mice appear to show some degree of tau hyperphosphorylation, they do not develop NFTs. Thus, the implications of decreasing tau phosphorylation on NFT formation for any therapeutic approach cannot be assessed in this model. Other transgenic mice, which overexpress tau alone or tau and APP, have been reported to form tangle-like structures and may therefore be useful tools for assessing potential therapeutics on NFT formation in vivo [54-56]. However, to date, the activation of kinases in these models has not yet been characterized.

p38 MAPK activation In Amyloid-beta

The in vitro effect of Aß on p38 in neurons is also controversial with a debate on whether Aß activates p38 in neurons. One research group has reported that Aß activates p38 in N2 neuroblastoma cells [7], while two other groups have not reported any such effect [57,58]. The recent finding that p38 is activated in double transgenic mice expressing AßPP (K670N/M671L) and PS1(P264L) [59], as determined by immunobloting, has shown that Aß activates p38 in vivo. However, due to the lack of concurrent immunocytochemistry data, it is not clear whether this is microglial or neuronal in origin. Neuronal accumulation of Aβ has been implicated as a cause of the neuronal loss that occurs in AD while previous studies have shown that Aβ is cytotoxic to neurons, at least in cell culture. The mechanisms and signaling pathways involved are just beginning to be unraveled. It has been reported that Aβ induces the activation of p38 in a concentration-dependent manner in both M17 human neuroblastoma cells and primary cortical neurons. Since Aβ is present at up to micromolar concentration with the development of amyloidal deposits, these findings suggest that the chronic exposure to high Aβ levels may also be responsible for the abnormal activation of p38 in AD brain [60,61]. Some studies have demonstrated that inhibition of the p38 pathway either by overexpressing the dominant negative p38 or by specific pharmacological inhibitor such as SB203580 results in decreased Aβ-mediated cytotoxicity indicating an important role for p38 in the toxication of Aβ. However, since overexpression of dominant negative p38 or application of SB203580 does not completely block Aβ-induced neuronal death, it is likely that p38 regulates neuronal death in concert with other signaling transduction pathways. In this regard, previous studies demonstrate that a related pathway, namely the JNK pathway, is also activated in cultured neuronal cells after exposure to Aβ and that inhibition of JNK also partially attenuates Aβ-induced cytotoxicity [57,58,62,63]. Therefore, it is conceivable that both the JNK and p38 pathways work synergistically in mediating Aβ-induced neuronal death. In support of such a concept, another reports demonstrated a nearly complete overlap between phospho-JNK and phospho-p38 in severe AD cases implying

that JNK and p38 are both activated by the same signal and, as such, work synergistically in vivo [60,61]. It will now be of great interest to establish the mechanism by which Aβ induces the activation of p38. In this regard, since Aβ appears to bind to the surface of neurons through multiple receptors, and one or more of them may be involved in Aβ-induced p38 activation, it is anticipated that the different receptors involved may lead to distinct responses. For example, the receptor for advanced glycation end products (RAGE), which interacts with Aβ may be a good candidate that is specifically involved in mediating Aβ-induced oxidative stress through the p38 pathway [64]. Also it is notable that Aβ binding of AβPP induces AβPP dimerization which, in turn, activates ASK1/MKK6/p38 cascade. It will also be important to characterize the mechanisms by which p38 activation leads to cell death. One possible target is TNF-α, because the expression of TNF-α is regulated by p38 [65]. More relevantly, the levels of both TNF-α are elevated in AD [66,67]. Therefore, the characterization of specific receptors as well as the downstream targets involved in Aβ-mediated events will not only help to better understand the nature of Aβ action but also identify specific targets for interrupting the pathogenesis process.

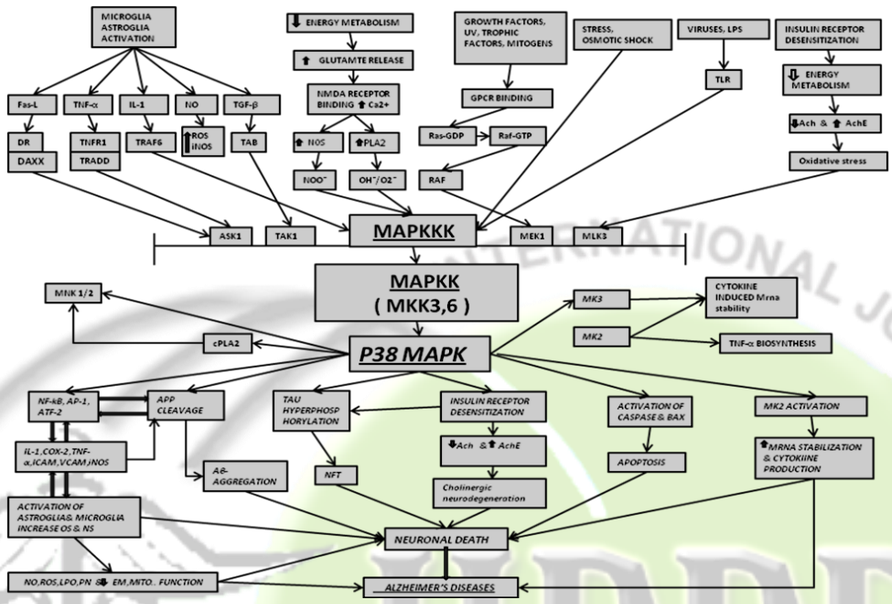

Fig- Neuronal death via activation of p38 MAPK

p38 MAPK activation In Long Term Potentiation

p38 MAPK has been reported to have higher expression in the hippocampus [29,68-70] and activation of p38 MAPK during stress conditions is reported to cause both short term and long term synaptic depression (LTD) [46,47,71-73]. But inhibition of p38 MAPK activity blocks the induction of LTD without affecting induction of LTP [42,46,70,74-77]. It has further been shown that there is complete absence or little formation of LTP induced by high frequency stimulation, whereas the low frequency stimulation enhances the formation of LTD in the hippocampus of STZ-induced diabetic rats [78-81].

p38 MAPK activation In Neuroinflammation

The activation of the p38 pathway plays essential role in the production of proinflammatory cytokines which has an integral role in Alzheimer's disease development and may precede plaque and tangle formation [14,82]. Inflammatory components related to AD neuroinflammation include brain cells such as microglia and astrocytes and p38 MAPK is involved in the activation of microglia and astroglia cells known to generate beta-amyloidal protein (Aβ) - one of the main pathologic features of AD [13,83]. Causative linkages between MAPK pathway activation and proinflammatory cytokine production by glia are based mainly on cell culture studies [18]. Phosphorylated p38 MAPK immunoreactivity was detected in microglia cells and co-localization with astrocytes in response to injury, illness, ageing or ischemia that begins a cascade of events which can be characterized as an inflammatory process [29,84]. In AD, the release of proinflammatory cytokines and interleukins via activation of p38 MAPK is stimulated in activated microglia and astrocytes and these cells are characteristically found near damaged neurons and plaques [82,85,86]. Glia cells normally mediate the innate immune response in CNS, but when activated, they produce inflammatory mediators like cytokine S100β, IL-1, IL-6, TNF-α, prostaglandins and leukotriens, which increase the Aβ activation. Aβ, in turn, increases the levels of these cytokines which lead to plaque and tangle formation. The cytokines can simultaneously activate p38 MAPK to induce the generation of other mediators like nitric oxide (NO) toxic to neurons in AD brain [73,87-89]. It has also been demonstrated in in vitro models of inflammation that inducible COX-2 and inducible nitric oxide synthase expression requires the activation of p38 MAPK signaling pathway. A large number of research reports have provided evidences that support the involvement of inflammatory process as one of the key cascades in the development and worsening of Alzheimer's disease in which p38 MAPK signaling pathway has been fully implicated [16,19].

p38 MAPK activation In Oxidative Stress and Excitotoxicity

Oxidative stress is the key feature for neuron cell death in AD [90](Butterfield et al., 2006) and p38 MAPK is highly sensitive to oxidative stress [91,92]. The oxidative stress induces several other key events like protein aggregation [93,94], mitochondrial dysfunction [95] and glutamate excitotoxicity [43], all of which combinedly contribute to the death of neurons due to imbalance between free radical production and degradation [83]. In AD, mitochondrial dysfunction plays a

potential role in cell death in which disturbance of energy metabolism leads to glutamate excitotoxicity [96,97]. The disturbed energy metabolism also enhances oxidative stress via excessive Ca^{++} influx in the cell leading to free radical production through p38 MAPK activation [15,16,98,99].

Moreover, p38 activation has been further demonstrated to be involved in cell death mechanisms in neuronal models. Treatment of neuronal cultures with arsenite, lipopolysaccharide, glutamate, amyloidal beta, IL-1, TNF- α, ceramide and sulfidryl oxidizing agent results in p38 MAPK activation [38,100,101]. In AD brain, neurons become particularly sensitive to attack by free radicals. Various free radicals like reactive oxygen species (ROS) and reactive nitrogen species (RNS) such as peroxynitirte lead to lipid peroxidation, protein oxidation and DNA damages [102,103,104].

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Abbreviations

Ad	Alzheimer's disease
Aβ	Amyloid beta
Ache	Acetylcholinesterase
Als	Amyotrophic lateral sclerosis
Ampa	A-amino-3-hydroxy-5-methyl-4-isoxazole propionate
App	Amyloid precursor protein
Ap-1	Activator protein-1
Ask1	Apoptosis-signal regulating kinase 1
Atf	Activating transcription factor
Atp	Adenosine triphosphate
Bmk1	Big mapk1
Csaids	Cytokine suppressive anti-inflammatory drugs
Chat	Cholineacetyltransferase
Chop	Caat enhancer binding protein homologous protein
Cox	Cyclooxygenase
Creb	Camp response element binding protein
Csf	Cerebrospinal fluid
Cns	Central nervous system
Cpcsea	Committee for the purpose of control and supervision of experiments on animals
Ddit3	Dna damage age inducible transcript3e
Elf-4e	Initiation factor-4e
Elk1	Ets like gene 1
Erks	Extracellular signal-regulated kinases
Fad	Familial alzheimer's disease
Fgf	Fibroblast growth factor
Gaba	Gamma amino butyric acid
Gsk	Glycogen synthase kinase
Gsh	Glutathione
Hsp	Heat shock protein
Hmg-14	High morbidity groups
H2b	Histone 2b
Il-1	Interleukin-1
Ial	Initial acquisition latency
Iaec	Institutional animal ethics commitee
Inos	Inducible nitric oxide synthase
Igf	Insulin like growth factor
Icam	Intracellular adhesion molecule
Icv	Intracerebroventricular
Jnk	C-jun n-terminal kinase
Lox	Lipoxygenase
Lps	Lipopolysaccharide
Lts	leukotrienes
Ltp	long term potentiation
Ltd	long term depression
Madd	Mitogen activated kinase activating death domain protein
Mapk	Mitogen-activated protein kinase
Mapkk	Mitogen-activated protein kinase kinase
Mda	Malondialdehyde
Mhc-ii	Major histocompatibility complex-ii
Mk2	Map kinase-activated protein kinase 2 or mk2
Mef-2c	Myocite enhanced factor 2c
Mekk	Mapk-extracellular signal-regulated kinase or mkkk
Mlk	Mixed lineage kinases
Mkk	Map kinase kinase
Mkkk	Map kinase kinase kinase or mekk
Mkp	Map kinase phosphatase
Mnk	Mapk signal integrating protein kinase
Mrna	Messanger ribonucleic acid
Msk	Mitogen and stress activated
Nfat	Nuclear factor of activated t-cells
Nf-κb	Nuclear factor kappa b
Nhe	Na+ - h+ exchanger isoform-1
Nft	Neuro fibrillary tangle
Nmda	N-methyl-d-aspartate
Phf	Paired helical filament
Prak	P38 regulating activated kinase
Pd	Parkinsonian diseases
Pdgf	Platelet derived growth factor
Pla2	Phospholipase a2
Pgs	Prostaglandins
Ps1	Presenelin1
Ros	Reactive oxygen species
Rns	Reactive nitrogen species
Rtl	Retention transfer latency
Sad	Sporadic alzheimer's disease
Sap1	Srf accessory protein
Sapk	Stress activated protein kinase
Stat	Signal transducer and activation of transcription 1a
Stz	Streptozotocin
Tak-1	Transforming growth factor–beta activated protein kinase 1
Tab1	Tak1–binding protein
Tao	Thousand and one kinase
Thr	Threonine
Tgf	Transforming growth factor
Tlr	Toll like receptor
Tyr	Tyrosine
Tnf	Tumor necrosis factor
Tnfr	Tumor necrosis factor receptor
Traf	Tumor necrosis factor receptor-associated factor
Vegf	Vascular endothelial growth factor

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