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REVIEW ARTICLE

Role of Major Caspases in Neurodegenerative Diseases

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ABSTRACT

Caspases, specially 1,3,6 are enzymes that involve in inflammatory process *via* cytokines and interleukin 1β. It engages in various diseases including neurodegenerative diseases. In this review we focused to review the role of caspase-1 mainly on CARD/DED molecular modulation system, TNF-α and pro IL-1β affiliated to neuronal cell death that occurs in the Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD).

Keywords: Caspases, CNS disorder, neurodegeneration, taupathy, dopamine.

MECHANISM OF CASPASES IN NEURO-DEGENERATION

Caspases are protease enzymes that are involved in apoptotic cell death and also cause inflammation in neurons. Caspases belongs to relatively large family and is comprises of caspases *i.e*., caspase-1 to -12, where caspase-12 is known as the pseudo-caspase. Caspase-1/ Interleukin-1 changing enzyme (ICE) is a proteolytic enzyme that cleaves the precursor proteins, inflammatory cytokines interleukin 1β and interleukin 18 as well as the pyroptosis inducer Gasdermin D, into active mature peptides [1]. Both the inflammatory cytokines after changing to its active shape leaves from cell and then initiate inflammatory response in adjoining cells. Likewise, those inflammatory caspases are also perpetrator for cell dying *via* autocrine motion, where caspase-1 breaks the pro-IL-1 beta into a form which is considered to be active. The resultant secreted IL-1 beta is then interacts with IL-1 receptor to pledge loss of life signaling within the cellular [2].

In this article our major focus was on the pathway through which caspase-1 plays its specific role in neuronal cell death related to different neurodegenerative disease (AD, PD and HD).

SELECTION OF LITERATURE REVIEW

Published articles were searched from PubMed related to caspase-1 in connection to its role in pathogenic pathway from last 20 years. There were total 128 articles appeared with the relevant keywords (caspase 1 AND neurodegeneration). Out to those 107 articles were excluded and only 21 were selected. Relevant articles were reviewed in context to the neurodegenerative diseases and possible role of caspases. Articles related to genetic basis or secondary causes were excluded from the review.

PROGRESSION OF NEURODEGENERATION THROUGH CASPASE DEPENDENT MOLECULAR CASCADES

These caspases may be categorized into two groups in terms of their molecular modulation *i.e*., procaspases 1, 2, 4, 5, 9, 11, 12, and 13 (CARD) caspase recruiting domain and caspases 8 and 10 (DED) death effector domain. Outcome of various studies have been analyzed related to

neurodegeneration. Main focus was cascades commencing for the initiation of the apoptotic cell dying through multiple molecular pathways. In some situation the involved pathway showed different binding site having initiator caspases that comprises upstream caspases. The activity of caspase-1 in PD was evaluated by conducting a study on α-synuclein protein through Western blot analysis and MALDI-TOF mass spectroscopy showing inflammation in the pathogenesis of the disease. Either caspase-1 dominant negative transgene or inhibitors of synthetic peptide caspase indicates delayed onset of sickness, development of disease and enhances the survival possibilities in transgenic mouse model of HD. Inhibition of caspase-1 and deletion of their gene turned to rescue mouse models of PD induced by MPTP triggered toxicity. TNF-α is involved in mediation of caspase activation. In AD there was an escalation in mRNA expression of several forms of caspases such as 1-3 and 5-9, equated with normal brains. In a study conducted for HD it was observed that human striatum models and transgenic mouse models of HD showed self-cleavage *via* caspase-1 and 3 activities for disease progression which was detected in the brain specimens.

HUNTINGTON'S DISEASE (HD)

HD is among one of the progressive autosomal neurodegenerative diseases (3) with eventual cognitive impairment [4] finally leads to death [5]. In a study it has been observed that ischemic condition or a traumatic injury to the cerebrum plays a vital role in caspase-1 activation that leads to the apoptotic pathway neuronal cell death to occur. In chronic neuronal disease particularly, caspase-1 and 3 are the two main caspases tend to produce more abundantly. Caspase-1, a primary member of this family is responsible for cleavage of pro- IL-1b to mature and energetic shape of the cytokine [6]. Activation of caspase-1 indicates, binding of mature IL-1b to its type 1 receptor suggests an crucial function facilitating neuronal cellular loss [7]. HD is amongst 1 of eight diseases, in which the etiologic modification has been accompanied to be a CAG development encrypting for an odd polyglutamine elasticity within the gene prominent as a reason for the ailment [8]. Therapeutic strategy for future drug target is inhibition of caspase 1 [9].

PARKINSON'S DISEASE (PD)

PD is mainly recognized as the deficiency of dopamine, there are numerous reasons from chemical aspects to the involvement of genetic components [10, 11]. It is stated that the aggregation of α-synuclein leads to the improvement of Lewy our bodies is the considerable pathological trademark of PD [12]. In PD the basic characterization of disease referring to the aggregation of aSyn occurs following different pathways depending on the disease progression, as there is a role of neurotransmitter dopamine in the nerve terminal, which is disturbed due to the aggregation on aSyn and deprives the normal neurotransmission leading to the PD symptoms [13]. A study using Western blot analysis revealed that the amount of truncated aSyn amplified consistently with cumulative concentration of caspase-1, signifying the *in vitro* truncation of aSyn caspase-1 straight [14].

It is reported previously that caspase-9 is activated by toxic cytochrome C and results in apoptosis [15]. Study on Knock out mice revealed the direct role of caspase in neurodegeneration by means of excitotoxicity-induced neuronal injury [16]. Inhibition of caspase is considered as one of the potential targets for remedy of PD [17]. Studies on caspase also showed its neuroprotective role, it is believed that this protection could be temporarily [18, 19]. One viable reason for this could be drawn from study that verified that for the induction of caspase-independent necrotic cell death RIP1 is needed for signaling complex made out of TNF-R1-associated death domain protein (TRADD) [20]. As parkin is believed to be contributor of PD pathogenesis, although mechanism of this is still unknown, but the caspase blocker found to have protective role on pathway through which parkin causes cell death [21].

ALZHEIMER'S DISEASE (AD)

AD is on the whole cause of dementia, at around 70-80% people suffering from AD shows dementia, memory loss [22-24]. AD is irreversible and significantly affect the quality of life of the patient. Tau proteins and beta amyloid along with genetic predisposition are the chief contributor of this disease [25-27]. The initial step for lengthy pro domain caspases is contiguity made dimerization. It is known that such dimerization is *via* binding of adaptor proteins with the seasoned area caspase activation and recruitment area domain. And also with the death

effector area motifs *i.e*., DED caspases 8 & 10. Both intrinsic and extrinsic pathways are involved in the demise regulation of the neuronal cells thru apoptosis. It is notable to say that inflammasome tend to be activation level for caspase-1 [28]. In this regard numerous unique inflammasomes are expressed differentially in different cell types of N, these includes, LRR-, NACHT-, pyrin-domain containing proteins (NRLP) 1 and ICE protease activating thing [29]. miRNA changes in one of the causes that also contributes in the pathomechanism of PD and AD [30]. Study showed the cleaved caspase-6 in brain of AD patients [31]. Similarly, in another study it was found that caspase-9 activation resulted in tau aggregation, thus contributing in the progression AD [32]. Recently, it is reported that neuronally Enriched RUFY3 play their part in the degeneration of neuron specially the axonal part, in conjunction with caspase 3. *In vivo* studies proven by deleting RUFY3 provide protection from axonal degeneration [33].

CONCLUSION

Caspases involved with dispensation of inflammatory signals are also associated with neurodegenerative diseases. In particular, role of caspase-1 seems to be vital in neuronal cell death. Moreover, caspase-1 inhibition caused direct effect in declining the onset of symptoms of disease as well as disease progression in patients of AD, PD and HD.

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