REVIEW ARTICLE

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Potential of chromatin modifying compounds for the treatment of Alzheimer's disease

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Alzheimer's disease is a very common progressive neurodegenerative disorder affecting the learning and memory centers in the brain. The hallmarks of disease are the accumulation of β-amyloid neuritic plaques and neurofibrillary tangles formed by abnormally phosphorylated tau protein. Alzheimer's disease is currently incurable and there is an intense interest in the development of new potential therapies. Chromatin modifying compounds such as sirtuin modulators and histone deacetylase inhibitors have been evaluated in models of Alzheimer's disease with some promising results. For example, the natural antioxidant and sirtuin 1 activator resveratrol has been shown to have beneficial effects in animal models of disease. Similarly, numerous histone deacetylase inhibitors including Trichostatin A, suberoylanilide hydroxamic acid, valproic acid and phenylbutyrate reduction have shown promising results in models of Alzheimer's disease. These beneficial effects include a reduction of β-amyloid production and stabilization of tau protein. In this review we provide an overview of the histone deacetylase enzymes, with a focus on enzymes that have been identified to have an important role in the pathobiology of Alzheimer's disease. Further, we discuss the potential for pharmacological intervention with chromatin modifying compounds that modulate histone deacetylase enzymes.

Keywords: *Alzheimer's disease*; *histone acetylation*; *histone deacetylase inhibitor*; *Trichostatin A*; *sirtuins*; *resveratrol*

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Histone deacetylase (HDAC) inhibitors represent a new class of anticancer compounds. To date, suberoylanilide hydroxamic acid (SAHA, Vorinostat, Zolinza™) and depsipeptide (Romidespin, Istodax™) have been approved by the US Food and Drug administration (FDA) for the treatment of cutaneous T-cell lymphoma (1–4). Numerous clinical trials involving HDAC inhibitors, either as monotherapies or in combination with other anticancer modalities, are currently underway for both hematological and solid malignancies (5–7). The anticancer properties of HDAC inhibitors are relatively well known (5–7). Although not as thoroughly investigated, it is emerging that HDAC inhibitors may have clinical potential for non-oncological applications, including asthma, cardiac hypertrophy and neurodegenerative conditions (8–16).

The aim of this review is to focus on the therapeutic potential of HDAC inhibitors in Alzheimer's disease (AD). Alzheimer's disease is the most common form of dementia and given the aging population in Western societies, prevalence is expected to continue to grow (17). It is an age-related progressive neurodegenerative disorder affecting the cortex and hippocampus (learning and memory centers in the brain), and is considered to be a disease of synaptic dysfunction and loss (18–21). The hallmark features of AD are: 1) the accumulation of β-amyloid neuritic plaques resulting from aberrant cleavage of the amyloid precursor protein (APP); typically APP is cleaved by α-secretase however, it can be cleaved into a soluble and the highly insoluble β-amyloid fragments, by β- and γ-secretases and 2) neurofibrillary tangles formed by abnormally phosphorylated tau protein (17). Other characteristics of AD include direct neurotoxic effects by lipid peroxidation, protein oxidation and formation of radical species (oxygen and nitrogen), inflammation arising from microglia surrounding plaques, mitochondrial damage and altered mitochondrial distribution, abnormal calcium regulation and aberrant interaction between metals and β-amyloid (22–24). Although, cholinesterase inhibitors and an

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N-methyl-D-aspartate antagonist are currently approved by the FDA to assist in managing symptoms, the disease is currently untreatable (25–27). Therefore, there is intense interest in the investigation of novel compounds as potential therapeutics for AD. Chromatin-modifying compounds such as HDAC inhibitors have been shown to have beneficial effects in experimental models of AD. In this review, we provide an overview of histone deacetylase enzymes and their relevance to AD. Pharmacological modulation of these enzymes in the context of AD is discussed.

Sirtuins in Alzheimer's disease

Histone acetylation is regulated by the opposing actions of HDAC enzymes and histone acetyltransferases (HATs) (28–30). Briefly, HATs catalyze the addition of the acetyl group of acetyl-CoA to the ε-amino lysine residue of histone lysines resulting in an open, transcriptionally permissive, chromatin architecture (31, 32). The HDAC enzymes catalyze the opposite (removal of acetyl groups) resulting in a more condensed, transcriptionally repressive chromatin conformation (28). In addition, numerous non-histone protein substrates, with key cellular functions (e.g. chaperones, DNA repair proteins, cell motility proteins, transcription factors and co-regulators and signaling mediators) have been identified for HDAC enzymes (33–36). HDAC enzymes are categorized into two main families; the metal-dependent HDAC1–11 enzymes and the seven mammalian class III sirtuins.

The class III HDAC enzymes consist of the sirtuins (SIRTs) 1–7 which are homologous to the *Saccharomyces cerevisiae* silent information regulator 2 (Sir2) (Fig. 1) (37, 38). The sirtuins are nicotinamide adenine dinucleotide (NAD^+)-dependent enzymes. They deacetylate substrates via the consumption of NAD^+ releasing nicotinamide, O-acetyl-ADP-ribose and the deacetylated substrate (29). The sirtuins contain a 257 amino acid catalytic core domain and have differing N- and C-terminal tails and zinc-binding domains (37). Phylogenetically the sirtuins can be further sub-classified into four distinct classes (37, 38). Class I consists of SIRTs 1–3 and those found in yeast. SIRT 4 is the sole member of class II enzymes with homology to enzymes found in bacteria, insects, nematodes and protozoans (37). Class III consists of SIRT 5, with homology to prokaryotic enzymes. Class IV includes SIRTs 6 and 7 which have homologous enzymes distributed in plants, vertebrates and metazoans (37, 38). The sirtuins have differing subcellular localizations with SIRTs 3, 4 and 5 found in the mitochondria, SIRT 2 is primarily cytoplasmic and SIRTs 1, 6 and 7 are found predominantly in the nucleus (39, 40). SIRT 1 is mainly associated with euchromatin but also shares a degree of cytoplasmic localization (39, 40). SIRT 6 is associated predominantly with heterochromatin and SIRT 7 is localized in the nucleolus (39, 40). SIRTs 1, 3 and 5 are NAD^+ -dependent deacetylases. They catalyze the deacetylation of histone and non-histone substrates. SIRT 6 is an NAD^+-dependent ADP ribosyltransferase (ART) and catalyzes the ribosylation of mitochondrial proteins. SIRTs 2 and 4 are both NAD^+-dependent and ART enzymes. The properties of SIRT 7 are not well-defined (39).

To date, SIRT 1 has been the most extensively investigated of the sirtuin enzymes. It has been shown to

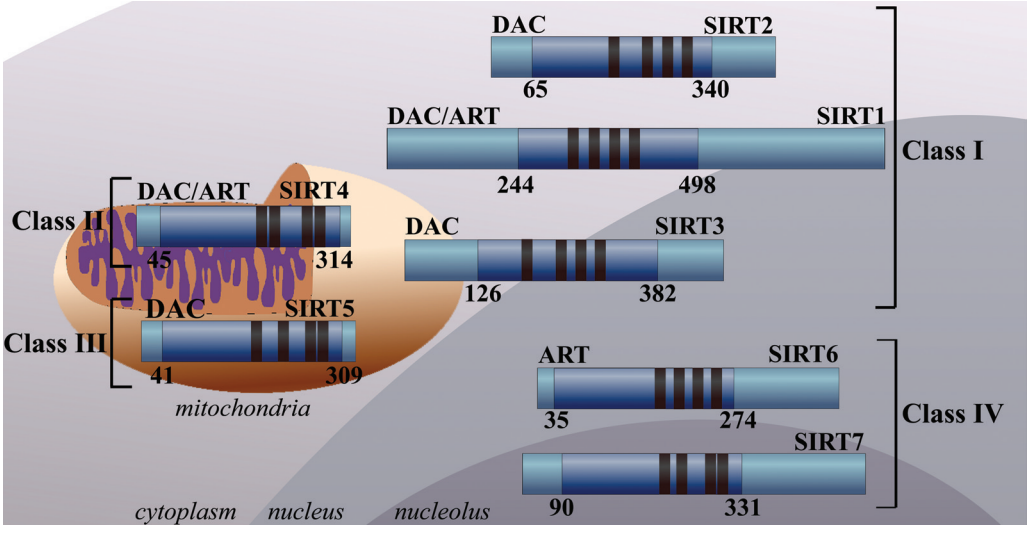

Fig. 1. Schematic representation of the class III sirtuin (SIRT) deacetylases. The sirtuins are highly conserved nicotinamide adenine dinucleotide (NAD+) dependent protein deacetylases (DAC) or ADP-ribosyltransferases (ART) which can be subdivided into four classes based on their phylogenetic lineage. The subcellular localization, DAC or ART binding domains (dark blue) and zinc binding domains (black) are depicted.

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modulate metabolism (e.g. via modulation of peroxisome proliferator-activated receptor gamma coactivator-1α [PGC-1α]), cellular stress resistance (e.g. by interaction with forkhead box class O (FOXO) transcription factors) and genomic integrity (e.g. by interaction with p53 and Ku70), which have been the subject of recent reviews (41–43). The functions of SIRT 1 in AD are summarized in Fig. 2. SIRT 1 has been shown to increase production of α-secretase, via deacetylation and activation of the retinoic acid receptor-β protein, which stimulates transcription of the *ADAM10* gene (44, 45). This results in the increases in *ADAM10* drive alpha-secretase cleavage of APP within the amyloid peptide region, resulting in the reduction of the β-amyloid peptide which gives rise to the characteristic amyloid plaques found in AD (44–46). ADAM10 also cleaves the cell-surface Notch receptor initiating the Notch signaling pathway which results in the upregulation of genes involved in neurogenesis (47).

Further, SIRT 1 has been shown to deacetylate the tau protein resulting in destabilization and proteolysis (48). This reduces neurofibrillary tangles in neurons (48). Another effect of SIRT 1 in AD is mediated by inhibition of NFκB signaling in microglia resulting in the decrease of β-amyloid-induced release of neurotoxic chemokines, cytokines and nitric oxide (47, 49). Anti-apoptotic effects are mediated by interaction with p53 and antioxidant effects of SIRT 1 are mediated by activation of FOXO3 and regulation of PGC-1α (42, 47). Resveratrol, a natural polyphenol abundant in the skins of red grapes and putative SIRT 1 activator, has been shown to have efficacy in relevant models of AD (Fig. 2) (50–56). Previous studies have found protective effects of resveratrol on beta-amyloid-induced toxicity in cultured rat hippocampal cells (57–59). Supplemental forms of resveratrol are undergoing evaluation in clinical trials for the disease. However, there are still question marks over its precise mechanism of action and whether the effects are mediated through activation of SIRT 1. Further, bioavailability of both oral resveratrol and its active metabolites remains controversial and it will be important to determine whether these reach biologically relevant concentrations to affect either sirtuin-dependent and/or independent pathways. Paradoxically, nicotinamide, a competitive sirtuin inhibitor has also shown beneficial effects in an animal model of AD, attenuating cognitive deficit (60). The mechanism was ascribed, at least in part, to reduced phosphorylation of tau protein at threonine-231 (T231) (60). Hyperacetylation of α-tubulin was also observed (60). These findings highlight the need for further clarification of the function of sirtuins in AD.

Metal-dependent histone deacetylases

The remaining 11 HDACs are typically referred to as the classical metal-dependent enzymes which require coordination of a divalent metal ion (zinc) for their catalytic activity (Fig. 3) (6, 7, 61, 62). These HDAC enzymes are divided into class I (HDAC1, 2, 3 and 8), class IIa (4, 5, 7 and 9), class IIb (HDAC6 and 10) and class IV (HDAC11) on the basis of their homology to yeast proteins (6, 7, 61, 62). Class I enzymes share homology with *Saccharomyces cerevisiae* transcriptional regulator RDP3 whereas class II enzymes are homologous with yeast Hda1 (62). HDAC11 shares homology with both class I and II enzymes and is the sole member of class IV (62). Class 1 enzymes are expressed ubiquitously, primarily localized in the nucleus and have important roles in cellular proliferation and survival (63). Class IIa enzymes shuttle between the nucleus and cytoplasm and

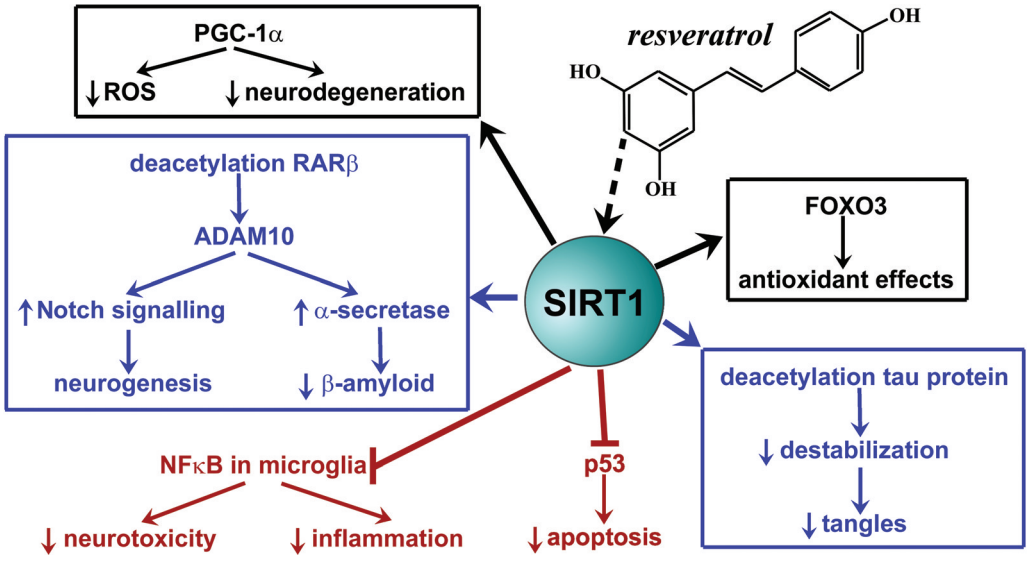

Fig. 2. Identified roles of sirtuin (SIRT) 1 in Alzheimer's disease. Although there a still controversies surrounding its precise mechanism of action, activation of SIRT 1 by the natural antioxidant resveratrol, may lead to the molecular effects depicted.

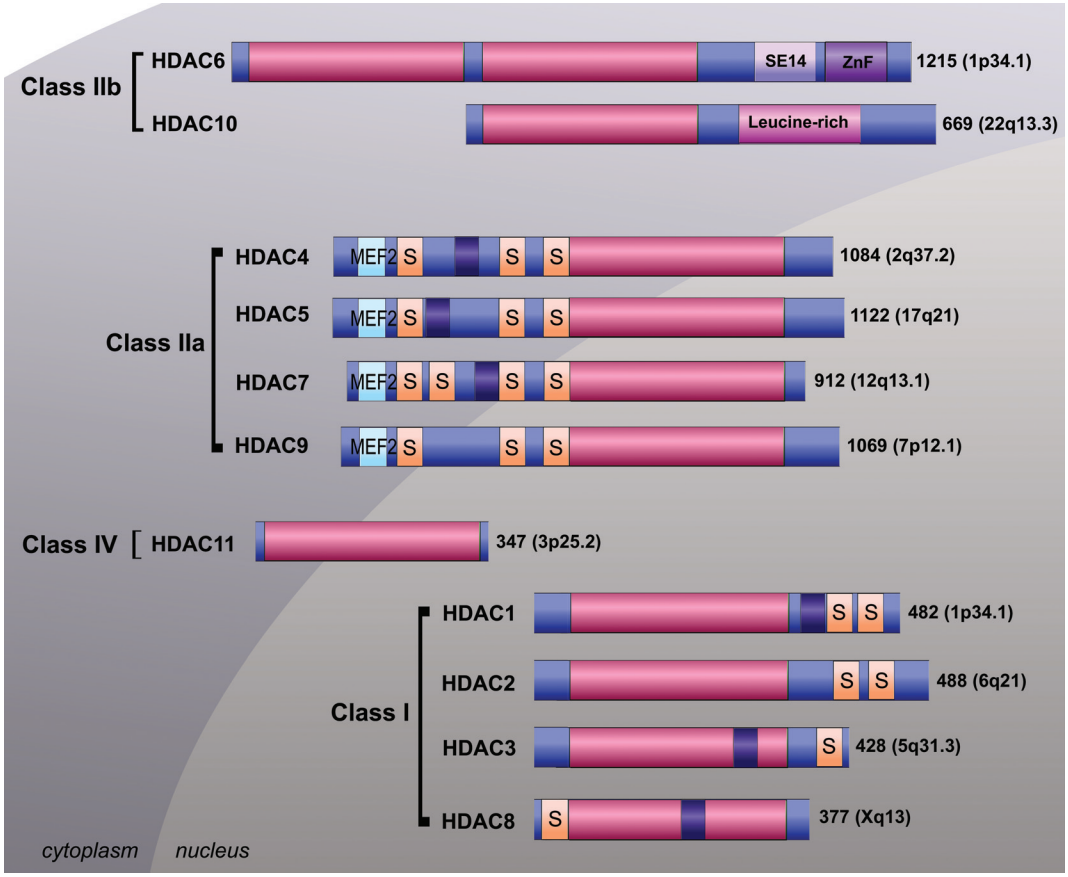

Fig. 3. Schematic representation of metal–dependent histone deacetylase (HDAC) enzymes. The classical HDACs are categorized into class 1 (HDAC1, 2, 3 and 8), class IIa (HDAC4, 5, 7 and 9), class IIb (HDAC6 and 10) and class IV (HDAC11) on the basis of their homology to yeast proteins. The deacetylase catalytic domain (pink), nuclear localization signal (purple), myocyte enhancer factor 2 binding domain (light blue), serine binding motif (orange). SE14 = serine–glutamate tetradecapeptide, ZnF = zinc finger protein binding domain and leucine rich domain are depicted. Subcellular localization is shown.

have more restricted tissue distributions and functions (6, 7, 35, 36, 61, 62, 64, 65). Little is known about the class IIb HDAC10. However, HDAC6, another class IIb member, is a major cytoplasmic protein with numerous identified non-histone substrates and important roles in aggresome formation and growth signaling (66–68).

With respect to AD, the class I HDAC2 and class IIb HDAC6 enzymes, have been associated with the pathobiology of the disease. Firstly, a seminal study has indicated that over-expressing HDAC2 in neurons in mice results in decreased synaptic plasticity and memory formation that modifying HDAC2, indicating that modification of HDAC2 could be a beneficial treatment for the memory impairment that occurs in AD (69). In the same study it was shown that HDAC2 deficiency exhibits the opposite effects indicating that the enzyme has an important role in negatively modulating synaptic plasticity, learning and memory (69). A solid body of evidence has accumulated for the role of HDAC6 in various neurodegenerative conditions including AD (70). Firstly, HDAC6 has been shown to be over-expressed in the brains of AD patients (by 52% in cortices and 91% in hippocampi) (71). In the same study it was shown that HDAC6 binds with tau protein both *in vitro* and in human brain tissues (71). Tau was identified as a HDAC6 deacetylase inhibitor (72). A further study, using the HDAC6 selective inhibitor, tubacin, has indicated that inhibition of the enzyme results in attenuation of tau phosphorylation at T231, which is important for the regulation of the stability of the cytoskeleton; this may decrease neurofibrillary tangle formation in AD (71, 73). Additionally, abnormal mitochondrial transport is a feature of AD, and it has been identified that HDAC6 has an important function in the modulation of mitochondrial transport through an association with glycogen synthase kinase-3β GSK3β (17, 74).

Histone deacetylase inhibitors in Alzheimer's disease

A structurally disparate group of compounds have been identified to possess HDAC inhibition activity. The prototypical Trichostatin A and the clinically approved

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SAHA are part of the hydroxamic acid class of HDAC inhibitors with HDAC inhibition activity in the nanomolar to low micromolar range (2, 6, 7, 33, 61, 75). The cyclic peptides, which include trapoxin and clinically approved depsipeptide, are also potent HDAC inhibitors. Similarly, the benzamides such as entinostat and electrophilic ketones such α-ketomide are potent HDAC inhibitors (2, 6, 7, 33, 61, 75). Aliphatic acids which include valproic acid, butyrate and phenylbutyrate are the least potent group of HDAC inhibitors possessing inhibition activity in the millimolar range (75–78). These compounds are typically referred to as broad-spectrum (pan-) HDAC inhibitors. Although they inhibit multiple HDAC1–11 enzymes they do possess some selectivity for HDAC isoforms. It is becoming apparent that selectivity or isoform-specificity is important particularly when considering non-oncological applications. Therefore, there is an intense effort aimed at development of such compounds, the HDAC6 specific, tubacin and the HDAC8 selective PC-34051 being pertinent examples (79–82).

There is accumulating evidence indicating the potential benefits of classical metal-dependent HDAC inhibitors in models of AD. For example, Trichostatin A has been shown to increase diminished H4 acetylation and improve contextual performance in a mouse model of AD (83). Similarly, the clinical hydroxamic acid, SAHA, has been shown to rescue contextual memory in a transgenic mouse model of AD (84). However, most studies to date have focused on the aliphatic acid group of HDAC inhibitors. Although histone acetylation was not considered, valproic acid has been shown to inhibit the production of β-amyloid in cells (HEK293) transfected with the Swedish APP isoform (APP_{751}) (85). Further, using the PDAPP (APP (V717F)) transgenic model of AD, valproic acid was shown to inhibit the production of β-amyloid in the brains of mice at biologically relevant doses of 400 mg/kg (85). Similarly, valproic acid has been shown to decrease β-amyloid production and to attenuate behavioral deficits in APP23 transgenic mice (86). Inhibition of GSK3β was suggested as a mechanism of action of valproic acid in AD (85). In another study, the beneficial effects of valproic acid in models of AD have been linked with histone acetylation (H4) (84). Valproic acid is particularly interesting given that it is relatively well-tolerated and has a very long history of clinical use as an anti-epileptic (87–89). However, the findings from a recent clinical trial indicate potential contraindications with the use of valproic acid in Alzheimer's disease highlighting the need for further research with this commonly used compound (90).

The aliphatic acid HDAC inhibitor, phenylbutyrate, has also been investigated in models of AD. Several groups have shown beneficial effects upon AD pathology and memory performance with no signs of toxicity in AD transgenic mouse models (84, 91–94). Further, phenylbutyrate specifically represses apoptosis in stressed neuronal systems (95–97). Findings have indicated that the beneficial effects of phenylbutyrate (increased synaptic plasticity, improved learning and memory and attenuation of spatial memory deficits) may be attributed to restored acetylation of histone H4 and to the clearance of intraneuronal Aβ accumulation (91, 92).

Although acetylation of histone H4 appears to be important in AD, the potential use of classical HDAC inhibitors in neurodegeneration remains controversial. Broad-spectrum HDAC inhibitors have cell-specific effects and are well-known for their potential to induce cell-death, apoptosis and cell-cycle arrest in malignant and transformed cells (7, 75, 98, 99). However, similar effects have been observed in neuronal cells (100). In this context, evaluation of more selective or isoform-specific compounds is important. In particular, HDAC2 and HDAC6 have been shown to have important roles in the pathobiology of AD (69, 70). Although there is no specific inhibitor of HDAC2 available, tubacin is highly selective for HDAC6 (79). As described earlier, tubacin has been shown to interact with tau protein (71).

Conclusions

Overall, the class III sirtuin deacetylases, in particular SIRT 1, have been shown to be important potential targets in AD. Numerous clinical trials, using resveratrol to target SIRT 1 are ongoing. The findings from clinical studies and further characterization of the sirtuins in relevant model systems are anticipated to improve our understanding of the therapeutic promise of targeting this class of enzymes in AD. Similarly, classical metal-dependent HDAC inhibitors have been shown to have beneficial effects of models of AD. While most studies have used relatively broad-spectrum inhibitors, it is becoming apparent that more selective or isoform-specific compounds may be more applicable. Evaluation of HDAC expression in animal models of disease akin to the atlas of the HDAC1–11 expression produced in normal rat brain will assist identifying relevant targets (101). Further genetic studies and experiments with more selective compounds (e.g. tubacin for HDAC6 and a selective HDAC8 inhibitor is available) are also required to clarify the roles of HDAC1–11 in the pathobiology of AD.

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