

# Electrochemical (Bio) Sensing of Amyloid Beta Peptide (A $\beta$ ) using Metallic Nanoparticles

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## ABSTRACT

Amyloid- $\beta$  (A $\beta$ ) peptides, the dominant factor of the aged plaques in brain of Alzheimer's disease (AD) patient, have been considered as the main biomarkers and curative targets for the diagnosis and prognosis of AD. The aggregation of A $\beta$  is concluded to be a precarious point in the pathogenesis of AD. Latterly, electrochemical systems have been strongly employed to selectively detect sorts of A $\beta$  moieties and monitor the oligomerization and assembly of A $\beta$  due to their high sensitivity, simplicity, brisk response, and compatibility with miniaturization. Hence, in this minireview, we outlined the advance in electrochemical (bio)sensing capped with metallic nanoparticles of A $\beta$  peptides species.

**Abbreviations:** AD: Alzheimer's Disease; NPs: Metallic Nanoparticles; APP: Amyloid Precursor Protein; LTP: long-term Potentiation; CSF: Cerebro- Spinal Fluid; MMSE: Mini-Mental State Examination; ER: Endoplasmic Reticulum; AICD: APP Intracellular Realm; GNPs: Gold Nanoparticles; AAO: Anodic Aluminum Oxide; SPCE: Screen Printed Carbon Electrode; CNTs: Copper Nanoparticles; SWV: Square Wave Voltammetry; ACSF: Artificial Cerebrospinal Fluid; EIS: Electrolyte-Insulator-Semiconductor; FETs: Field-Effect Transistors; NW: Nanowire; PABA: p-Aminobenzoic Acid; CAb: Capture Antibody; LOD: Limit of Detection; MIPs: Molecularly Imprinted Polymers;

## Mini Review

Electrochemical techniques are suitable for in situ detection of molecules, due to their high sensitivity, simplicity, reproducibility, low cost, the relatively low time resolution and the direct analysis without the use of extraction steps or preconcentration. Moreover, they can easily be used in small devices (miniaturization) [1]. Electrochemical detection is usually based on monitoring the signal of the oxidation or reduction of electroactive groups at the electrode surface [2,3]. Thus, the construction of the electrode is critical step in the identification of analytes. Mercury is electrode among the most widely used electrodes, utilized in electroanalytical techniques [2]. Although the use of this electrode gives a low detection limit, nevertheless presents some inherent disadvantages. On one hand, the toxic mercury causes pollution of the environment and serious adverse effects in humans and secondly, the existing soluble oxygen has a serious effect on the reduction signals and it must be completely removed from the solution prior to assay. Thus, efforts

are made to formulate the existing electrodes in order to generate new less toxic and with improved properties electrodes, using electrode surface modification. Metallic nanoparticles (NPs) due to their physical properties [4] i.e. biocompatibility, high conductivity and high surface to volume ratio, are commonly capped with a variety of matrices in order to expand their applications in nanomaterials, biomedical [5] and sensors [6] or electrochemical (bio)sensors [1,7-13], making them excellent candidates in fabricating nanoscale devices. Generally, the synthesis of NPs by the reduction of the metal in solution involves two steps such as nucleation and growth [14].

The rate of nucleation and growth of NPs decides the dimension of the final products. NPs have been synthesized by various chemical reduction methods using ascorbic acid, citrate and NaBH<sub>4</sub> [15]. But these methods require huge quantity of chemicals and controlling the particle size is difficult. Sunlight, on the other hand, acts as an

external motivator to control the size of NPs, which would provide sufficient energy to get the particle of the required size. In addition, sunlight is nontoxic, nonpolluting and simple in chemical processes [16]. In comparison to stabilizers such as plant leaves [17], fruit extracts [18], plant roots [19], glucose [20] and carbonate materials [21] used in the NPs composition, organic and natural dyes [14,22-26] have specific ionic, polar, non-bond functional groups (- azo dyes, - sulfites, - hydroxyl and - nitro groups) and are usually systems that have  $\pi$ -conjugates [27] capable of being polymerized. Amyloid beta peptide ( $A\beta$ ) is a natural product of low abundance in the healthy brain and is produced through the proteolytic processing of a transmembrane protein, amyloid precursor protein (APP), by  $\beta$ - and  $\gamma$ -secretases [28].  $A\beta$  accumulation in the brain is proposed to be an early toxic event in the pathogenesis of Alzheimer's disease (AD) [29], which is the most common form of dementia associated with plaques and tangles in the brain. Currently, it is unclear what the physiological and pathological forms of  $A\beta$  are and by what mechanism  $A\beta$  causes dementia.

Meanwhile, there is currently no cure for AD and no reliable method of diagnosis other than post-mortem brain examination. Therefore, the development of appropriate detection methods for AD is an urgent requirement, in order to provide earlier diagnosis and, thus, useful therapeutic intervention. As a severe neurological disorder, Alzheimer's disease (AD) leads to progressive memory loss and cognitive impairment [30]. Although many details associated with AD pathology are still unknown, the deposition of extracellular beta-amyloid ( $A\beta$ ) peptide residues was regarded as one of the main hallmarks in the brain [29].  $A\beta$  is a natural product of low abundance in the healthy brain, where it is cleaved out of the neuronally-expressed amyloid precursor protein (APP) by sequential action of beta and gamma secretase enzymes [31]. After the cleavage of the APP induced by  $\beta$ - and  $\gamma$ -secretases,  $A\beta$  forms with a largely hydrophilic N-terminal domain and a C-terminal hydrophobic domain [32]. Of these  $A\beta$  species,  $A\beta$ 1-40 and  $A\beta$ 1-42 composed 40 and 42 amino acid residues dominate. In contrast to  $A\beta$ 1-40, the amount of  $A\beta$ 1-42 decreases significantly but it displays more neurotoxic resulting from the presence of the two additional hydrophobic amino acids [33]. Thus, the low-level  $A\beta$ 1-42 is always considered as a promising biomarker for AD diagnosis.  $A\beta$ 1-42 monomers tend to aggregate into the oligomers or fibrils under different external stimuli including oxidation stress and metal ions. The aggregated ones of  $A\beta$ 1-42, especially  $A\beta$ 1-42 oligomers, are believed as major toxic effects in AD which could be considered as promising biomarkers or aggregation inhibitor-based drug targets for AD therapy [34]. Of the monomeric, oligomeric and fibrillar forms of  $A\beta$ , a plethora of evidence now indicates that soluble  $A\beta$  oligomers ( $A\beta$ O) are the major neurotoxic species in AD.  $A\beta$ O bind to neurons, particularly at the post-synaptic membrane, causing synaptic dysfunction, blocking key processes which underlie memory and learning (e.g. long-term potentiation; LTP) and causing neurotoxicity and cell death at low concentrations [35].

The level of  $A\beta$ O in the brain, particularly those with a "fibrillar" conformation, correlate with AD onset and severity much more strongly than the insoluble fibrillar load [36]. Importantly,  $A\beta$ O have been detected in animal models of AD before the phenotypic presentation of disease [37]. The development of more sensitive diagnostic tests to detect very low levels of biologically relevant  $A\beta$ O could ultimately lead to clinically useful tests for pre-symptomatic diagnosis and monitoring of AD progression, either before or during disease onset and throughout therapeutic intervention. Measuring  $A\beta$ O in a patient, reflects that the  $A\beta$ O count in patient fluids (i.e. blood and cerebro-spinal fluid; CSF) reflects the most direct and relevant biomarker for AD [38]. Levels of  $A\beta$ O in plasma and CSF samples have been shown, by ELISA and flow cytometry, to be elevated in AD and correlate with Mini-Mental State Examination (MMSE) scores [39]. However, many ELISA-type assays have not been able to detect  $A\beta$ O in CSF, although  $A\beta$ O were detected in AD brain samples [40]. Crucially, it was shown that levels of  $A\beta$ O in serum correlate directly with the CSF  $A\beta$ O load, demonstrating that a blood test type assay for  $A\beta$ O is relevant to the  $A\beta$ O content in CSF [41].

Measuring  $A\beta$ O levels in patient fluids by conventional laboratory techniques such as ELISA-type assays is time consuming and expensive. Problems related to the diagnosis and monitoring of AD underscore the need of developing new diagnostic methods using easier-to-use, low-sample volume approaches. These requirements are met by electrochemical methods, which are a reliable and profitable appliance for the determination of  $A\beta$ , in order to facilitate their use in the diagnosis and monitoring of this disease, due to their ease of use, simplicity, selectivity, sensibility and low cost [42,43]. As it can be seen by the lack of literature, electrochemical sensors have been rarely used in the detection of  $A\beta$  peptide and AD diagnostics. Therefore, electrochemical (bio)sensors capped with metallic nanoparticles for the determination of  $A\beta$  are summarized in this short review.

### Alzheimer's Disease (AD)

Alzheimer's disease is outlined by the irregular accumulation of  $A\beta$  protein, which is crucial for recollection and perception, in the brain sectors.  $A\beta$  is a regular product of the cellular metabolism obtained from the amyloid precursor protein (APP). APP is manufactured in the endoplasmic reticulum (ER) and then carried to the Golgi complex, where it matures and is finally transferred to the plasma membrane. Mature APP at the plasma membrane is cleaved by the consecutive activity of the  $\beta$ -secretase and  $\gamma$ -secretase to produce  $A\beta$  [44]. The freshly developed  $A\beta$  either is delivered to the extracellular space or lingers correlated with the plasma membrane and lipid raft networks. The wind up of  $A\beta$  to ganglioside GM1 in the lipid rafts heavily promotes  $A\beta$  aggregation [45]. The binding of ApoE to  $A\beta$  is taken up by the cells through receptor-mediated endocytosis arbitrated by LRP (LDL receptor-related protein), and LDLR controls aggregation but further the cellular uptake of  $A\beta$  [46].

Endocytosed A $\beta$  still has entry to more subcellular containers through the vesicular transport system. Previous investigations led to A $\beta$  fibrils as the neurotoxic promoter forcing cellular downfall, recollection failure, and additional AD attributes [47]. Over the last two decades, farther research has recommended that oligomeric or prefibrillar species of the A $\beta$  peptide are the most harmful to neuronal cells. Soluble A $\beta$  can tie up to numerous particles in the extracellular zone, incorporating cell surface receptors, metals and cellular membranes [47]. In that sense, AD pathogenesis incorporates both A $\beta$ -dependent and A $\beta$ -independent procedures. There are still countless uncertainties about the actual pathogenesis of AD and the  $\beta$ -amyloid beneficence to the outbreak of the disease. A $\beta$  or A $\beta$  oligomers or plaques are not exclusively at fault for the outbreak of the disease [47]. The “type London” amyloid precursor protein (APP) mutations, inducing simply a slight rise in  $\beta$ -amyloid generation, provoke the outbreak of the pathology sooner than the “type Swedish” mutations, prompting a more immense raise of the protein [48], proposing that there are alternative processes engaged in the outbreak of AD.

Indeed, the A $\beta$ -independent procedures are interceded through APP, intracellular parts and PS1 through the cellular processes, such as inflammation, oxidative stress and Ca<sup>2+</sup> dysregulation, affected in AD pathogenesis [49]. Cdk5 may be influenced by or collaborate with both paths, and its activation brings about DNA corruption, cell cycle activation and neurodegeneration [50]. Non-A $\beta$  elements such as Tau and ApoE also assist to AD pathology [51]. All these paths can prompt synaptic dysfunction, neurodegeneration and AD. The aged plaques, likewise, are not implied to be a sole component of Alzheimer’s disease. They broaden with senility, even in healthy people, and the number of plaques in healthy controls is usually proportionate with the count located in age-matched affected persons [52]. Besides,  $\beta$ -amyloid is physiologically formed in healthy brains during neuronal activity and is mandatory for synaptic flexibility and recollection [53]. Along, in the AD culture, there is particularly a powerless interrelationship among the count of aged plaques and the severity of the pathology. The cleavage of APP by  $\gamma$ -secretase provides some portions named AICD (APP intracellular realm), which turns up to present an influential function in the outbreak of AD. In fact, it is experienced that transgenic mice for AICD exhibit tau phosphorylation and aggregation and decreased cell proliferation/survival, even in the absence of endogenous APP [54]. Large elevations of AICD may further present an influential aspect in the pathology of human brain [55].

There are considerable alternative challenging assumptions, such as the cholinergic hypothesis, the tau hypothesis, and the hypothesis that some extra environmental hazard aspects, may grant to supplementary origins of the disease [56]. The cholinergic assumption recommends that AD is induced by cholinergic effects similar to the decreased synthesis of the neurotransmitter acetylcholine, or to the induction of substantial

aggregation of amyloid and to the neuroinflammation [57,58]. The vast majority of ready for use therapies lie on this supposition [59]. The tau assumption posits that tau protein irregularities set up the disease avalanche as hyperphosphorylated tau forms neurofibrillary tangles, forcing fragmentation of microtubules in brain cells [60], emerging in malfunctioning of the biological activity among neurons and later in the downfall of the cells. Alternative suppositions incorporate environmental liability aspects like smoking and infection, as well as a neurovascular assumption, which implies that the blood-brain barrier is precarious for brain A $\beta$  homeostasis and controls A $\beta$  carriage through the LRP receptor and RAGE [61].

### Electrochemical (bio)sensing using metallic nanoparticles

So far, many attempts have been made for detection of A $\beta$ , using other analytical methods such as mass spectrometry, capillary electrophoresis, surface plasmon resonance (SPR) and so on [38,62]. However, most of these methods suffered from expensive, time-consuming, labor intensive. Neuro imaging methodologies namely MRI, PET, SPET, NIR, SPR, and SPRI, are capable to detect A $\beta$  in bio-fluids to monitor AD progression and pathogenesis. Nevertheless, these methods are limited to clinics due to requirement of sophisticated equipment and high expertise to operate. Biosensors offer a much more rapid, cost-effective highly sensitive method of analyte detection at the point-of-care. Several efforts to generate a laboratory based A $\beta$  biosensor have been made recently although none of these systems is specific for A $\beta$ 0 due to the nature of the bioreceptors employed. For example, Stravalaci and colleagues sought to develop an SPR-based assay that recognizes specifically A $\beta$ 0, however, their use of the pan-A $\beta$  antibody 4G8 as bioreceptor would also recognize other A $\beta$  aggregation states as well as APP and its metabolites in patient samples [63]. An electrochemical biosensor which utilized a ferrocene-conjugated peptide as bioreceptor was shown recently to detect synthetic A $\beta$ 0, however there was also some recognition of monomeric A $\beta$  and the system was not tested using biologically relevant species [64]. To overcome these short comings, electrochemical sensing methodologies are being investigated for rapid, selective and sensitive detection of A $\beta$ .

Moreover, the challenges to determine A $\beta$  (1-42) in plasma is in what manner the detection limit will be lowered down to 10 pg mL<sup>-1</sup> since A $\beta$  (1-42) levels in plasma in patients with AD and controls were detected from 25 to 85 pg mL<sup>-1</sup>. The sensitivity of a biosensor counts on the amount of analytes that can be adhered on the sensor’s electrode. Late advances in micro/nanotechnologies have raised the linkage process [65,66]. Nanomaterials contribute a considerably enormous surface area than that of bulk material or thin film and have been handled to enhance the detection signal of biomedical devices [67,68]. On this basis, Wu et al. [69] described a nanostructured biosensor, relied on electrochemical impedance

spectroscopy (EIS) with evenly accumulated gold nanoparticles (GNPs) as the sensing electrode for the efficient detection of A $\beta$  (1-42). An anodic aluminum oxide (AAO) layer with a nano hemisphere design was utilized as the substrate. A gold thin film was altered onto the AAO substrate to function as the electrode GNP deposition and the sensor for A $\beta$  (1-42). A $\beta$  (1-42) antibody was formulated, and its specificity with A $\beta$  (1-42) was established by Western blot. They scanned the aggregation of A $\beta$  (1-42) at 1 g mL<sup>-1</sup>. The morphology of A $\beta$  (1-42) was in the pattern of round aggregates with diameter of around 1500–2000 nm.

EIS measurements for nanostructured biosensors were utilized to determine the concentration of A $\beta$  (1-42). The plot for the dependence of EIS concentration measurement ended in an equation  $\Delta R_{ct} = 29098 \log [A\beta (1-42)] + 90150$  with an R<sup>2</sup> value of 0.9916. The linear detection range was between 1 pg mL<sup>-1</sup> and 10 ng mL<sup>-1</sup> of A $\beta$  (1-42). The detection limit was found to be equal to 0.01 pg mL<sup>-1</sup>. Furthermore, Diba et al. [70] constructed an electrochemical immunosensor engaging the creation of a surface sandwich complex on a gold nanoparticle (AuNP) modified screen printed carbon electrode (SPCE) for the femtomolar determination of A $\beta$  in both serum and plasma. Both bio receptors composing the assessment are eminently selective antibodies for A $\beta$ , specifically anti A $\beta$  (12F4) and (1E11) which enjoy distinct binding sites for the A $\beta$  peptide. In order to advance the sensing performance for complex biological fluidic matrix analysis, various mixed monolayers of thiol modified polyethylene glycol (PEG) and mercaptopropionic acid (MPA) were self-assembled onto the AuNP-SPCE followed by binding anti A $\beta$  (12F4) to MPA utilizing a heterobifunctional cross linker. Surface sandwich complexes of anti A $\beta$  (12F4)/A /anti A $\beta$  (1E11)-ALP were then composed through subsequent adsorption with the latter anti A $\beta$  (1E11) associated to alkaline phosphatase (ALP) enzyme. The reaction of surface clogged ALP with the substrate, 4-aminophenyl phosphate (APP), provoked voltammetric detection signals that linearly furthered as a function of A $\beta$  concentration. Differential pulse voltammetry was administered to provide the lowest detectable concentration of 100 fM of A $\beta$  with a linear response range from 100 fM to 25 pM.

Following optimization, the immunoassay platform was administered in diluted human serum and plasma samples to determine the native concentration of A $\beta$  and the outcomes were verified utilizing a commercially accessible ELISA test. A disposable electrochemical immunosensor for the determination of amyloid-beta 1-42 was established by Costa Rama et al. [71]. Screen-printed carbon electrodes nanostructured with gold nanoparticles engendered "in situ" were handled as the transducer surface. The immunosensing strategy dwelt in a competitive immunoassay: biotin-amyloid-beta 1-42 immobilized on the electrode surface and the analyte (amyloid-beta 1-42) contend for the anti-amyloid-beta 1-42 antibody. The electrochemical detection was driven out utilizing an alkaline phosphatase labelled anti-rabbit IgG

antibody. The analytical signal was laid on the anodic stripping of enzymatically provoked silver by cyclic voltammetry. The immunosensor exhibited a low limit of detection (0.1ng/mL) and a broad linear range (0.5–500 ng/mL). Another auspicious application performed by Moreira et al. [72] represented the construction of a state-of-the-art mediator-free electrochemical sensor, incorporating an electrochemically active element at the carbon-working electrode. For this direction, carbon nanotubes were modified with copper nanoparticles (CNT-CuO) and shield on the carbon-area. This electroactive film additionally served as substrate to compile the biorecognition feature. As proof-of-concept, the 3-electrode arrangement was composed sensitive to the peptide  $\beta$ -amyloid 42 (A $\beta$  -42), by mobilizing a plastic antibody on top of the electroactive film.

The plastic antibody was retrieved by eletropolymerizing aniline (ANI) at neutral pH, under the existence of the template (A $\beta$  -42). Afterward, the template molecule was expelled from the polymeric grid by acidic treatment. The unfilled sites retrieved saved the shape of the imprinted protein and were capable to rebind new peptide molecules. SEM, XRD and RAMAN studies were carried out in order to handle the surface modification of the carbon electrode. The capability of the biosensor to rebind A -42 was scanned by square wave voltammetry (SWV). Redox peaks were gathered at +0.4 V and peak currents reduced for an increasing concentration of A $\beta$  -42. The reproducibility of the analytical signal was 8.37 %, given in terms of the relative standard deviation of an A $\beta$  -42 standard solution of 1.0 ng/mL. The detection limit was 0.4 ( $\pm 0.03$ ) pg/mL. The utilization of the device was assessed in serum samples, spiked with A $\beta$  -42 from 1.0 to 66.0 ng/mL. The obtained recovery data ranged from 88 to 93 %. The strongest accomplishment of this task associated to the withdrawal of a redox probe reading-stage in electrochemical biosensing, by merging the electroactive element within the working electrode. Additionally, the fabricated biosensor exhibited outstanding properties in terms of response time and simplicity, revealing a noteworthy capability for on-site utilization in medical research and clinical diagnosis.

One more study [73], were ported a simple and sensitive electrochemical strategy for the detection of total A $\beta$  peptides using gold nanoparticles modified with A $\beta$  (1-16)-heme(denoted as A $\beta$ (1-16)- heme-AuNPs). Monoclonal antibody (mAb) specific to the common N-terminus of A $\beta$  was immobilized onto gold electrode for the capture of A $\beta$ (1-16)-heme-AuNPs. The anchored A $\beta$ (1-16)- heme-AuNPs showed strong electrocatalytic O<sub>2</sub> reduction. Preincubation of the mAb-covered electrode with native A $\beta$  decreased the amount of A $\beta$ (1-16)-heme-AuNPs immobilized onto the electrode, resulting in the decrease of the reduction current of O<sub>2</sub> to H<sub>2</sub>O<sub>2</sub>. The competitive assay is sensitive and selective to A $\beta$  peptides. The voltametric responses were found to be proportional to the concentrations of A $\beta$  ranging from 0.02 to 1.50 nM, and a detection limit of 10pM was achieved. To demonstrate the viability

of the method for the analysis of A $\beta$  in real sample, artificial cerebrospinal fluid (aCSF) containing A $\beta$ (1-40), A $\beta$ (1-42) and A $\beta$ (1-16) was tested. We believe that the method would offer a useful means for quantifying A $\beta$  in a biological matrix, and be valuable in the design of new types of electrochemical biosensors for the detection of peptides and proteins. A noticeable study [74], reported the prosperous presentation of a label-free application for the detection of amyloid-beta (A $\beta$ ) peptides by exceptionally selective aptamers immobilized onto the SiO<sub>2</sub> surface of the constructed sensors. A modified single-stranded deoxyribonucleic acid (ssDNA) aptamer was specifically fashioned and synthesized to detect the target amyloid beta-40 sequence (A $\beta$ -40).

Electrolyte-insulator-semiconductor (EIS) structures as well as silicon (Si) nanowire (NW) field-effect transistors (FETs) coated with a thin SiO<sub>2</sub> dielectric layer have been strongly functionalized with A $\beta$ -40-specific aptamers and utilized to detect ultra-low concentrations of the target peptide. The fastener of amyloid-beta peptides of various concentrations to the surface of the sensors differed in the range from 0.1 pg/mL to 10  $\mu$ g/mL deriving from a change of the surface potential was recorded by the invented devices. Furthermore, the single-trap phenomena detected in the new Si two-layer (TL) NW FET structures can be forcefully utilized to raise the sensitivity of nanoscale sensors. The electrochemical sensing of saccharide-protein interactions using a couple of sialic acid derivatives and Alzheimer's amyloid-beta (A $\beta$ ) is described [75]. The densely-packed saccharide area for recognition of protein was fabricated onto a carbon electrode by three steps, which were electrochemical deposition of Au nanoparticles on a screen printed strip, self-assembled monolayer (SAM) formation of the acetylenyl group on Au nanoparticles, and the cycloaddition reaction of an azide-terminated sialic acid to the acetylenyl group. The attachment of A $\beta$  peptides to the sialic acid layer was confirmed by electrochemistry and atomic force microscopy imaging. The intrinsic oxidation signal of the captured A $\beta$ (1-40) and (1-42) peptides, containing a single tyrosine (Tyr) residues, was monitored at a peak potential of 0.6 V (vs. Ag/AgCl within this sensor) in connection with differential pulse voltammetry. The peak current intensities were concentration dependent. The proposed process provides new routes for analysis of saccharide-protein interactions and electrochemical biosensor development.

Another study [76] describes a new sensitive strategy for the determination of tau protein, involving a sandwich immunoassay and amperometric detection at disposable screen-printed carbon electrodes (SPCEs) modified with a gold nanoparticles-poly(amidoamine) (PAMAM) dendrimer nanocomposite (3D-Au-PAMAM) covalently immobilized onto electrografted p-aminobenzoic acid(p-ABA). The capture antibody (CAb) was immobilized by crosslinking with glutaraldehyde (GA) on the amino groups of the 3D-Au-PAMAM-p-ABA-SPCE, where tau protein was sandwiched with a secondary antibody labeled

with horseradish peroxidase (HRP-DAb). Amperometry at -200 mV (vs the Ag pseudo-reference electrode) upon the addition of hydroquinone (HQ) as electron transfer mediator and H<sub>2</sub>O<sub>2</sub> as the enzyme substrate was utilized to detect the immunocomplex evolution. The high analytical performance of the immunosensor in relation of selectivity and low limit of detection (LOD) (1.7 pg mL<sup>-1</sup>) favored the direct determination of the target protein in raw plasma samples and in brain tissue extracts from healthy human beings and post mortem diagnosed AD patients. An innovative sandwich assay electrochemical biosensor was established in the literature [77] for extraordinarily sensitive and selective determination of A $\beta$ 0, utilizing molecularly imprinted polymers (MIPs) and aptamer as the indication item.

Rather of practicing an antibody to notice the A $\beta$ 0 target molecules, the A $\beta$ 0 in the samples were occupied by the film of MIPs and the A $\beta$ 0-specific aptamer, composing a MIPs/target/aptamer sandwich strategy for the highly selective detection of A $\beta$ 0. The A $\beta$ 0-specific aptamer was immobilized on the surface of core-shell nanoparticles that incorporated silver nanoparticles with silica nanoparticles (SiO<sub>2</sub>@Ag NPs). The profoundly sensitive electrochemical signal from the sandwich method was developed by utilizing a short load of A $\beta$ 0 to prompt huge count of electrochemically active Ag NPs. Under the optimized conditions, the biosensor exhibited satisfying linearity in the concentration range of 5 pg mL<sup>-1</sup> to 10 ng mL<sup>-1</sup> with a limit of detection of 1.22 pg mL<sup>-1</sup>. The biosensor further revealed superlative specificity, reproducibility and stability. In extension, the usefulness of detecting A $\beta$ 0 in human serum was profitably proved, indicating the up-and-coming capability of this biosensor for clinical research and the early diagnosis of AD.

A colorimetric immunosensor was described in the literature [78], adopting antibody modified-silver nanoparticles (AgNPs) for the specific detection of A(1-40/1-42), which directly can be considered as analytical tool for preclinical diagnosis of Alzheimer's disease, depended on the interaction between -amyloid and Cu<sup>2+</sup>. AgNPs surface was coupled with C-terminal antibody of A(1-40/1-42)(Ab-AgNPs). In the presence of Cu<sup>2+</sup> and A(1-40/1-42), the Ab-AgNPs offered large specificity to A(1-40/1-42), and hence Ab-AgNPs solution markedly aggregated due to the fastener of Cu<sup>2+</sup> with -amyloid, leading to pronounced colour switch from yellow to red. In comparison to previous practices that engaged antibodies, this system showed great merits of visualization, appliance, and simplicity. By adopting the immunosensing technique, the A(1-40/1-42) could be detected with a detection limit of 86 pM. An excessively sensitive and profoundly straightforward aptasensor was constructed for the quantitation of amyloid beta (A $\beta$ ) by electrochemical transduction of a fern leaves-like gold nanostructure [79]. The gold nanostructure was incorporated by electrodeposition employing polyethylene glycol 6000 as a shape-directing agent, and characterized electrochemically and by field

emission scanning electron microscopy. A specific RNA aptamer was immobilized on the fern leaves-like gold nanostructure, and binding with A $\beta$  was detected by the ferro/ferricyanide redox marker. The aptasensor was skilled to detect A $\beta$  in a linear range of 0.002–1.28 ng mL<sup>-1</sup> and a limit of detection of 0.4 pg mL<sup>-1</sup>. The aptasensor was interference-free, and for manifestation of its viability for A $\beta$  determination in real samples, the human blood serum and artificial cerebrospinal fluid containing A $\beta$  were tested.

An outstanding example of A $\beta$  peptide biosensors is describing the general idea of designing electrochemical biosensors with peptide probes as the receptors of targets and the inducers of gold nanoparticles (AuNPs) assembly on electrode surface [80]. To prove the usefulness of this sensor, human chorionic gonadotropin (hCG) was initially detected as a model analyte. Specially, the hCG-binding peptide prompted the aggregation of AuNPs in solution; by modifying the electrode with the hCG-binding peptide, the peptide-induced AuNPs assembly was accomplished on the electrode surface, rising in the production of a network of AuNPs and a powerful decline of charge transfer resistance. The connection of hCG onto the electrode surface through the probe-target interaction forced the peptide fail its strength to prompt the production of the AuNPs-based network architecture on the electrode surface, hence getting an enlarged charge transfer resistance. The electrochemical impedance technique favoured for the determination of hCG with a detection limit 0.6 mIU/mL. Moreover, the process was utilized to the selective detection of amyloid-oligomer. The development of interdigitated microelectrodes (IMEs) as an impedance biosensor for the blood-based A $\beta$  detection utilizing gold nanoparticles (AuNPs) sandwich method is proposed in the literature [81].

It contributed logarithmically linear sensitivity and improvements in the detection limits of approximately 2.87-fold and 74.84 %, respectively. mouse plasma sample from the blood of double-mutated APP/PS1 transgenic (TG) and wild-type (WT) mouse group was used, and AD diagnostic capability was investigated by A $\beta$  detection in the plasma samples. The findings exhibited that AuNPs sandwich strategy supported A $\beta$  detection strongly discerned TG and WT mouse groups. Hence, with this sensor, A $\beta$  was detected with high sensitivity and selectivity. An exceptionally sensitive electrochemical impedance sensor for amyloid beta oligomer (A $\beta$ O) was constructed utilizing a cellular prion protein (PrPC) bioreceptor associated with poly(thiophene-3-acetic acid) transducer [82]. A supplementary thin layer of poly(3,4-ethylene dioxythiophene) inserted with gold nanoparticles was engaged to equip large electrical conductivity and a broad surface area. The sensing performance was searched in relation to sensitivity and detection range. The sensor showed remarkably low detection limit at a subfemtomolar level with a broad detection range from 10<sup>-8</sup> to 10<sup>4</sup> nM and its feasibility was confirmed in mice infected with Alzheimer's disease (AD). A straightforward and sensitive electrochemical method for the selective detection of A $\beta$ O using

silver nanoparticles (AgNPs) as the redox reporters and PrP(95–110), an A $\beta$ O-specific binding peptide, as the receptor is disclosed [83]. Specially, adamantine (Ad)-labeled PrP(95–110), tagged as Ad-PrP(95–110), caused the aggregation and color switch of AgNPs and the follow-up production of a network of Ad-PrP(95–110)-AgNPs.

Then, Ad-PrP(95–110)-AgNPs were anchored onto a  $\beta$ -cyclodextrin ( $\beta$ -CD)-covered electrode surface through the host-guest interaction between Ad and  $\beta$ -CD, thus forming an amplified electrochemical signal through the solid-state Ag/AgCl reaction by the AgNPs. In the existence of A $\beta$ O, Ad-PrP(95–110) combine specially with the A $\beta$ O, thus dropping the power to bind AgNPs and to bring about the production of an AgNPs-based network on the electrode surface. Therefore, the electrochemical signal ebbed with a raise in the concentration of A $\beta$ O in the range of 20 pM to 100 nM. The biosensor enjoyed a detection limit of 8 pM and exhibited no response to amyloid- $\beta$  monomers (A $\beta$ M) and fibrils (A $\beta$ F). An unusual shaped microporous gold nanostructure with a regular size of 150 × 250 nm was electrodeposited on a polycrystalline gold surface at 0 mV (vs. AgCl) using sodium alendronate is illustrated [84]. The nanostructure was then characterized by field-emission scanning electron microscopy. An electrochemical peptide-based biosensor was constructed by immobilizing an A $\beta$ (1–42)-binding peptide on the gold nanostructure. Attaching of A $\beta$ (1–42) by the peptide was screened electrochemically utilizing ferro/ferricyanide as a redox probe. Differential pulse voltammograms in a potential range of 0–500 mV (vs. AgCl) with regular peak potentials at 224 mV are linear in the 3–7000 pg mL<sup>-1</sup> A $\beta$ (1–42) concentration range, with a 0.2 pg mL<sup>-1</sup> detection limit.

The biosensor is without interference and was administered to the quantitation of A $\beta$ (1–42) in artificial cerebrospinal fluid and spiked serum samples. Sun et al. [85] developed an electrochemical hydrogel biosensor depended on gold NPs (GNPs) and graphene oxide to screen A $\beta$ O. To set up an A $\beta$ O nano sensor, the thiolated cellular prion protein (PrPC) peptide probe was immobilized on the constructed electrode. The unambiguous coupling between PrPC probes and A $\beta$ O on the hydrogel electrode has advanced the resistance of electron transfer. The biosensor performed a large accuracy for the detection of A $\beta$ O. It could selectively discriminate A $\beta$ O from fibrils or monomers of the amyloid beta (A $\beta$ ). Additionally, recognition of A $\beta$ O (as low as 0.1 pM) in blood plasma or artificial CSF was remarkably sensitive. The linear range for the detection of A $\beta$ O was between 0.1 pM - 10 nM. Multifactorial paths and different bio-molecular interactions influence AD. Accordingly, to advance performance, AD should be managed with a mixed diagnosis of numerous activities. Kim et al. [86] disclosed a remarkably responsive nano sensor for detection of  $\tau$  (tau) protein, Amyloid-beta 1–40, and Amyloid-beta 1–42 biomarkers on a single nanoplatform formed on gold nanoparticles and LSPR impact without supplementary procedures for complicated partition from

various samples and marker identification. The detection limit for amyloid-beta ( $A\beta$ ) 1–40,  $A\beta$  1–42, and  $\tau$  protein was 34.9 fM, 26 fM, and 23.6 fM, respectively (in mimicked blood under physiological condition). It has been proposed that gelsolin ties up to both  $A\beta$ (1–40) and  $A\beta$ (1–42) in a concentration dependent aspect [87].

Thus, Shi's group described two "sandwich-like" electrochemical biosensors for the detection of  $A\beta$ (1–40/1–42) peptides in the CSF and varied brain regions with gelsolin as the biorecognition item [88,89]. Screen-printed carbon electrodes modified with multiwalled carbon nanotubes (MWCNTs) and AuNPs were used for the immobilization of gelsolin and the follow-up capture of  $A\beta$ (1–40/1–42). In their prime work, the gelsolin-Au-thionine bioconjugates were utilized to notice the captured  $A\beta$ (1–40/1–42) moieties by the gelsolin- $A\beta$  interaction [88]. The concentrations of  $A\beta$ (1–40/1–42) peptides were detected by screening the electrochemical reduction of thionine (Th). In the second work, the HRP-Au-gelsolin nanohybrid formed by one-pot modification of AuNPs with horseradish peroxidase (HRP) and gelsolin was occupied as the nanoprobe for the realization of the captured  $A\beta$  species [89]. The binded HRP then catalyzed the oxidization of 3,3',5,5'-tetramethylbenzidine (TMB) substrate in the presence of  $H_2O_2$ , which formed a quantitative electrochemical signal. The detection limits of these two methods were 50pM and 28 pM, respectively. Varying from the past assays for  $A\beta$  detection, these practices counteracts the handling of antibodies for the apprehension and identification of  $A\beta$ .

## Conclusion

Electrochemical (bio)sensors capped with metallic nanoparticles for the determination of  $A\beta$  peptide are summarized in this mini review. Electrochemical (bio)sensors are relatively late outlets for reliable, accurate, sensitive, selective, green, cheap on the detection of  $A\beta$  peptide, engaged in Alzheimer's disease, and are in accordance to ongoing European and international advancements, regarding civil well-being affairs and portray the state of the art on flourishing analytical procedures. Additionally, inspecting the anticipations of strengthening the accuracy, the sensitivity, the selectivity, the simplicity as well as diminishing the cost and toxicity of the present  $A\beta$  peptide analytical tools is likewise an ingenious way to meet an elderly demand of clinical diagnostics and electrochemical (bio)sensor are convenient engines. Meantime, higher analytical traits are gained when electrochemical techniques are conjoined with NPs. To that end, the great antifouling feature of NP electrodes is particularly relevant, granting that they are experienced to accomplish a substantial number of detections without the fall of their analytical items as it has been acknowledged by their profitable repeatability. This precise attribute confers them satisfactory propensities to work out on the determination of biomarkers in real samples. Notwithstanding, the prevalent protest lingers to remain, when real samples are to be evaluated, due to complications associated to reproducibility, stability, as well as

interferences. These items can be treated by expanding state-of-the-art sensors which are coupled to NPs and electroactive mediators.

Once and for all, the cantankerous anticipations of the outstanding edge on the determination of  $A\beta$  peptide, certainly loft ingenious bounds on electrochemical sensors for brisk screening of a disease, triggering modern perceptions in diagnostics. An upcoming improvement in electrochemical sensing may be the expansion of implantable sensors for lengthened disease screening. Hence, novel (bio)materials must be incorporated into devices, managing stability and hindering infections. Recent determination methods, like ultra-fast CV may be employed for real-time  $A\beta$  peptide screening.

## Conflicts of Interest

The authors declare no conflict of interest and the funders had no role in the design of the study; in the writing of the manuscript, or in the decision to publish this review".

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