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PII: S0141-8130(20)33691-6

DOI: https://doi.org/10.1016/j.ijbiomac.2020.06.239

Reference: BIOMAC 15996

To appear in: *International Journal of Biological Macromolecules*

Received date: 26 April 2020

Revised date: 13 June 2020

Accepted date: 25 June 2020

Please cite this article as: M. Ameri, Z. Shabaninejad, A. Movahedpour, et al., Biosensors for detection of Tau protein as an Alzheimer's disease marker, *International Journal of Biological Macromolecules* (2018), https://doi.org/10.1016/j.ijbiomac.2020.06.239

Biosensors for detection of Tau protein as an Alzheimer's disease marker

Mehrdad Ameri[#1,2], Zahra Shabaninejad[3,4#], Ahmad Movahedpour[1,2#], Amirhossein Sahebkar[5,6], Soheila Mohammadi[7,8], Saereh Hosseindoost[9], Mohammad Saeid Ebrahimi[10], Amir Savardashtaki[1,2] *, Mohammad Karimipour[11,*], Hamed Mirzaei[12,*]

[1]*Department of Medical Biotechnology, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences Shiraz, Iran*

[2]*Student research committee, Shiraz University of Medical Sciences, Shiraz, Iran*

[3]*Department of Nanobiotechnology, School of Basic Science, Tarbiat Modares University, Tehran, Iran.*

[4] *Pharmaceutical Science Research Center, Shiraz University of Medical Science, Shiraz Iran*

[5]*Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran*

[6]*Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*

Nano Drug Delivery Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran

[8]*Pharmaceutical Sciences Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran*

[9]*Department of Neuroscience, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran*

[10]*School of Medicine, Kashan University of Medical Sciences, Kashan, Iran*

[11]*Department of Anatomical Sciences, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*

[12]*Research Center for Biochemistry and Nutrition in Metabolic Diseases, Institute for Basic Sciences, Kashan University of Medical Sciences, Kashan, I.R. Iran*

# Equal contribution with first author

* Corresponding Authors

Hamed Mirzaei. Research Center for Biochemistry and Nutrition in Metabolic Diseases, Institute for Basic Sciences, Kashan University of Medical Sciences, Kashan, I.R. Iran. Tel: +98-

31-55540022; Fax: +98-31-55540022; E-mail addresses: mirzaei-h@kaums.ac.ir & h.mirzaei2002@gmail.com

Amir Savardashtaki. Department of Medical Biotechnology, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences Shiraz, Iran; E-mail address: Dashtaki63@gmail.com

Mohammad Karimipour. Department of Anatomical Sciences, Faculty of Medicine, Tabriz University of Medical Sciences, and Tabriz, Iran; Tel:: +984133342086; Fax: +98 4133342086, Email: karimipourm@tbzmed.ac.ir, karimipourm@yahoo.com,

Abstract

Known as a main neural MAP (microtubule associated protein), tau protein contributes to stabilizing microtubules involved in cellular transmission. Tau dysfunction is mainly associated with neurodegenerative diseases, particularly Alzheimer's disease (AD). In these patients, all the six tau isoforms, which are in hyperphosphorylated form, are first aggregated and then polymerized into neurofibrillary tangles inside the brain. Tau protein detected in cerebrospinal fluid (CSF) is significantly correlated with AD and is well recognized as a hallmark of the disease. Served for detection of analytes of interest, biosensor device comprises a physical transducer and a keen biological recognition component. Qualitative and quantitative evaluations may be performed through analyzation of the data, which is gathered by measurable signals converted from biological reaction. Antibodies, receptors, microorganisms, nucleic acids, enzymes, cells and tissues, as well as some biomimetic structures, normally constitute the biosensor biological recognition part. Production of nanobiosensor, which was made possible through several accomplishments in nano- and fabrication technology, opens up new biotechnological horizons in diagnosis of multiple diseases. In recent years, many researches have been focused on developing novel and effective tau protein biosensors for rapid and accurate detection of AD. In this review, tau protein function and correlation with AD as well as the eminent research on developing nanobiosensor based on optical, electrochemical and piezoelectric approaches will be highlighted.

Keywords: Tau protein; Alzheimer disease; Optical nanobiosensor; Electrochemical biosensors; Piezoelectric nanobiosensor

Abbreviations

Aβ: amyloid β; aCSF: artificial CSF; AD: Alzheimer's disease; anti-Tau: antibody against Tau protein; AuNPs: Gold nanoparticles; CG: carboxyl grapheme; CNS: central nervous system; CSF: cerebrospinal fluid; DPV: differential pulse voltammetry; DTNB : 5, 5′-dithiobis-(2-nitrobenzoate); DTSSP: 3,3'-Dithiobis(sulfosuccinimidylpropionate); EDC/NHS: 1-ethyl-3- (3-dimethyl-aminopropyl)carbodiimide/ N-hydroxysuccinimide; GCE: glassy-carbon electrode; GO: graphene oxide; LSPR: Localized surface plasmon resonance; mAb2: monoclonal antibody2; MAP: microtubule associate protein; MAPT gene: Microtubules Associated-Protein Tau; MWCNTs: Multi-Walled Carbon Nanotubes; NFTs: neurofibrillary tangles; PQC: piezoelectric quartz crystal, P-Tau: phosphorylated Tau; QCM: Quartz crystal microbalance; SAM: self-assemble monolayer; SERS: Surface-enhanced Raman spectroscopy; SPR: surface plasmon resonance; Tau-FITC: Tau conjugated to fluorescein isothiocyanate; TH: Thionon

1- Introduction

Alzheimer's disease (AD) is a common neurodegenerative disorder with memory loss and damage of cognitive functions characterized by extracellular accumulation of amyloid β (Aβ) and neurofibrillary tangles (NFTs)/Tau tangles buildup inside neurons. Tau is a microtubule associated protein (MAP) which regulates microtubule dynamics and is necessary for axonal cargo transportation. The phosphorylated tau protein has a low tendency to bind microtubules and highly phosphorylation of tau leads to deposition of NFTs within dendritic spines and further inhibition of synaptic responses [1, 2]. Despite the seemingly growing details on molecular pathogenic mechanisms of AD with the discovery of Aβ and tau proteins , there is still limited data on the exact pathophysiology of AD and hence challenges remain in its appropriate treatment [3, 4].

It is complicated to discover of the underlying pathologic mechanism involved in AD based on its phenotype, therefore various biomarkers could be of great help to expedite early diagnosis of the disease [5]. Biomarkers are measurable indicators which are found during a particular phase of the disease that makes them beneficial for diagnosis as well as monitoring treatment response [6]. The well-known pathological biomarkers for AD are extracellular amyloid beta peptide (Aβ peptide) plaques and intracellular neurofibrillary tangles (NFTs) of hyperphosphorylated Tau [7-9]. Diagnosis of Alzheimer's disease has been largely advanced, since it has been found to be associated with an increase in total tau protein and phosphorylated tau protein levels and a decrease in amyloid peptide level in cerebrospinal fluid [7].

Biosensors are analytical tools for detection of biomolecules in samples and/or solution in a short time with high sensitivity and specificity. After capturing the desired target via a biorecognition element, a measurable signal will be generated due to the action of transducer [10]. Tau protein

is a biomarker for early detection of AD which has recently attracted much attention to develop various platforms and biosensors for detection of this protein in different samples.

In this review, we summarized developed biosensors for screening tau protein concentration inside samples as an early diagnostic biomarker for AD.

2-Tau and its biological function

Tau is a structural microtubule associated protein (MAP) that was discovered in 1975 as a regulatory factor for microtubule polymerization and stabilization [11]. Tau protein is encoded by *MAPT* (Microtubules Associated-Protein Tau) gene which is located on chromosome 17q21. Normally detected within CNS axons, Tau is involved in assembly and stabilization of microtubules which facilitates axonal transportation [12, 13]. Depending on the stage of neuronal maturation , 16 exons of *MAPT* gene can be randomly spliced [14, 15]. Among remarkable heterogeneities seen in tau variants, the hyperphosphorylated subtype is invariably accumulated in pathological lesions [14-16].

Phosphorylation of tau is the main factor for microtubule regulation. In humans, the shortest tau protein is expressed in fetus, whereas the longest isoforms are found in adults. In AD, the average **phosphate groups per tau molecules is increased and detaches the protein from microtubule [17, 18]**. Hyperphosphorylated tau molecules may result in: i) synaptic malfunction, ii) modified degradation during autophagy or inside a proteasome, iii) increased aggregation and iv) altered interaction with other associated molecules[15].

Abnormally hyperphosphorylated tau is the main contributor to form neurofibrillary tangles which are tau protein depositions comprised of paired helical and straight filament. Neurofibrillary tangles along with extracellular Aβ accumulation are two valuable markers for AD diagnosis [19].

3- Nanobiosensors for Tau detection

Biosensors are highly sensitive tools with simple operation, rapid response and low cost which contain two main parts: A bioreceptor that can recognize the biologic target and a transducer to convert the existence of analyte into a measurable signal [20]. In biorecognition phase, the favorable analyte will be detected followed by creation of a signal in form of heat, pH or light. The signal will then become measurable in transducing phase [21, 22]. Biosensors have been applied in disease monitoring, drug discovery and detection of various molecules including heavy metal ions or fluid biomarkers corresponding to a disease stage [23]. Biosensors reduce the target screening time and offer highly-sensitive reliable information on the intended target. [21]. The basic mechanism of action for a common biosensor is illustrated in **Figure 1**. In order to capture specific biomolecules, various substances are used such as enzymes, antibodies, aptamers, and whole cell [24]. Based on the type of transducer used for signal transmission and measurement, biosensors are classified into optical [25], thermometric [26], electrochemical [27], and piezoelectric biosensors [28]. Noble detection techniques are now highly benefiting from emergence of nanomaterial-based biosensors, which has put an end to former problems of conventional biosensors (e.g. sensitivity and selectivity) through modification of biorecognition layers.

However the expense and duration of process, as well as sensitivity and selectivity, still have to be improved throughout future investigations. In this regards, nanomaterials are also being incorporated in biosensor analytical tools to provide more sensitive and highly accurate nanobiosensor platforms. With the advent of various nanomaterials and their specific properties, sensing methods have remarkably improved.[29]. Various types of nanomaterials such as gold nanoparticles [30], magnetic nanoparticles[31], quantum dots[32], and carbon nanotubes[33]

have been added to biosensors and due to their unique chemical and physical characteristics, enormous changes in identification of biomolecules have been made [34].

Biosensors have shown to be a favorable method for early detection of AD biomarkers within the cerebrospinal fluid (CSF) [35]. Total tau protein and phosphorylated tau (P-Tau) are known as promising CSF biomarkers for early diagnosis of AD, therefore with adequate knowledge from the structure of these biomarkers, highly sensitive and specific biosensors could be created [36, 37]. Increased concentration of tau protein inside CSF samples indicates neurodegenerative disorders and axonal damages which makes it a target biomarker to screen for AD progression [4]. Various types of biosensors have been developed to detect tau proteins and are summarized as below (**Table 1**).

3-1- Optical biosensors

Optical biosensors are the most common biosensors containing a biorecognition element integrated with an optical transducer system. Reaction between analytes and biorecognition elements produces an optical signal which provides qualitative or quantitative measurement of the analyte [25]. The surface plasmon resonance (SPR) [44], fluorescent [45] and optical wave interferometry [46] have been used to determine this interaction. Over the years, numerous optical biosensors have been broadly developed for tau protein detection. Mainly, fluorescent-based optical biosensors offer promising analytical outcomes for various biologic analytes. There were some limitations in terms of using early fluorescence probes through past decades such as, low water solubility and stability; these defects were controlled by using proteins and enzymes for biochemical targets [47].

In 2017 Ao Huang et al [48] developed a fluorescent biosensor to identify tau protein with detection limit of 0.14 pmol/ml in the buffer. Specific antibody against tau protein conjugated on

graphene oxide (GO) nanosheets was used which could bind to both tau protein as the analyte and fluorescent Tau-FITC (Tau conjugated to fluorescein isothiocyanate) as the standard. These two forms of tau protein compete for the binding site on the antibody. GO has a great ability for energy transmission and due to its optical characteristics, it can be used as a fluorescence quencher via electron energy transmission even with additional modifications [49]. The concentration of tau protein present in a sample is directly proportional to the intensity of signal production .When tau protein is bound to the antibody, Tau-FITC molecules remain free in the solution and since the quenching effect of GO surface is removed, fluorescence signal will be enhanced. [48]. The schematic overview of this platform is illustrated in **Figure 2**.

The surface plasmon resonance (SPR) biosensors are optical platforms emerging rapidly through past decades and are shown to be highly sensitive tools to measure the desired target either qualitatively or quantitatively [49, 50]. SPR is a fundamental principle of many optical and color-based biosensors. In this technique, polarized light at specific angle or specific wavelength causes resonant oscillation of the conductive electrons at interference of two media, usually glass and liquid. when the analyte is attached on the surface of silver or gold nanoparticles, the refractive index is changed which can be measured by changes observed in radiation angle or wave length shifts **[51].** Localized surface plasmon resonance (LSPR) is a particular type of SPR in which the localized oscillation of electrons induces an electromagnetic field around the nanoparticle dielectric interface. Like SPR, the absorbed light wavelength or peak resonance absorbance changes by dielectric interface shifts [52]. The clinical required range for tau diagnosis is in picomolar range [5]. While most SPR biosensors are able to detect tau protein at nanomolar concentration levels, immuno-based SPR biosensors are developed which can amplify the detection signal and allow tau detection at picomolar concentrations.

Although a small number of studies have aimed for SPR-based tau biosensing [53-55], none of them were designed to determine tau protein level in CSF. Direct and sandwich-based methods were used during development of SPR immunosensor for tau detection in buffer and artificial CSF at nano-molar dosage. Gold NPs-DNA conjugates have effectively been used in DNA sandwich-like detection strategies for SPR signal amplification since the arrival of metallic nanostructures [56-58]. In addition, detection of tau protein were pursued by some other investigations through adding the enhancing properties of MWCNTs to a classic immuno-based sandwich format[59]. Though being largely studied in biosesnsing [60], this type of nanostructures are less employed for SPR [59].

Lisi et al. , who were inspired by such techniques, amino-coupled a secondary monoclonal antibody (mAb_2) to MWCNTs (MWCNTs-mAb_2) via a sandwich strategy, taking into account that tau clinical levels are significant at pM range [5]. These nanostructured amplifiers were successfully exploited for signal amplification, obtaining a gain of more than two orders of magnitude respect to the unlabeled strategy [61]. The preparation and use of MWCNTs-mAb_2 conjugates are here optimized to work within the tau picomolar range, and in these conditions the bioassay resulted reversible and with an estimated batch-to-batch variability of 14%. As a whole, they reported the preliminary but encouraging results on the use of MWCNTs-antibody conjugation for the improvement of the analytical performances of SPR sensing for tau detection in the picomolar range, and may open new roads for innovative and sensitive SPR-based methods [61].

Tau381, one of the six isoforms of tau protein (1N3R isoform), is regarded as a critical biomarker in early AD diagnosis [62]. SPR biosensor using DNA aptamer/antibody sandwich assay was developed for Tau381 detection in human plasma samples with a detection limit of 10

femtomolar. To perform sandwich method, an tau antibody is added after attachment of tau to the aptamers on the surface of a chip for further signal enhancement (**Figure 3**) [63]. However, some redundant signals are also generated from unspecific binding of molecules such as proteins and DNA to the gold surface that conceal the main signal from target analyte. Recording the signals prior to attachment of aptamers or other recognition elements is an authentic method to increase the specificity of outcomes [64, 65]. Another SPR platform for tau protein detection was developed using multimode optical fibers with a 40 nm-thick gold-covered core to immobilize antibodies against tau proteins on the surface of the sensor. This biosensor preserved tau detection in blood samples based on immunoreaction [66].

Raman scattering is a phenomenon that photons are scattered inelastically and is the basis of Surface-enhanced Raman spectroscopy (SERS), a molecular detection technique that enhances the Raman scattering when the target is absorbed on the surface of a rough metal or by nanostructures such as plasmonic-magnetic silica nanotubes [67].The electromagnetic field around nanostructure and nanomaterials significantly enhances the Raman spectroscopy signals . SERS based biosensors have shown to be a sensitive and promised platform for detection of analytes with low concentrations in solutions and several SERS biosensors for numerous molecules have been fabricated [68]. SERS biosensor for tau protein was developed with detection limit less than 25 femtomolar. This platform used functionalized magnetic silica nanoparticles and monoclonal anti-tau as capturing agents which are capable of attaching to tau protein inside the samples and functionalized gold nanoparticles with polyclonal anti-tau acting as SERS surface. Gold nanoparticles were activated by EDC/NHS polyclonal anti-tau layer attached to their surface. Also, 5,5-dithiobis (2-dinitrobenzoic acid) (DTNB) was used to cover the surface of gold nanoparticles and act as Raman reporter . Utilizing polyclonal anti-tau as

biorecognition element increased the intensity of signal in low concentration tau protein samples. Interaction of anti-tau with tau protein in solution resulted in aggregation of nanoparticles and produced a sharp peak at SERS spectrum due to DTNB coverage. Based on concentration of tau within the sample, peak height could vary [69]. This biosensor platform is schematically shown in **Figure 4**.

3-2 Electrochemical biosensors

Electrochemical biosensors are widely used platforms for detection of various targets such as blood glucose[70], microRNAs [71] and breast cancer biomarkers [72]. The interaction of target with recognition element generates an electric signal. Following further processing steps, they provide qualitative or quantitative information on the target analyte. They are favorable due to their low-cost , simplicity in operation, high sensitivity and able to detect analytes at extremely low concentrations [73, 74].Two types of electrochemical biosensors are available; biocatalytic and affinity sensors. In biocatalytic platforms, an enzyme acts as a sensing element and an electric signal is produced via a specific catalytic reaction whereas in affinity types, antibodies or nucleic acids are detecting elements [75].

Several types of targets such as bacteria, parasite, virus, protein and nucleic acid targets are identified by specific bonds with short ssDNA or ssRNA nucleic acid in vitro molecules, named aptamer [76, 77]. Particular types of interaction between complimentary strands, hydrogen bonds and electrostatic forces lead to the right 3D structure of these molecules. Detecting process may be done more effectively by aptamers than antibodies due to their higher rate of chemical stability, structural modification, affinity, specificity, and electrodes fixation density. Krylova et al. investigated aptamer matching with tau381, using affinity-mediated non-equilibrium\ capillary electrophoresis of equilibrium mixtures [42]. The dissociation rate Kd was 116 ± 6 nM

and the Kd value was found to be 116 _ 6 nM [78]. Therefore, aptamers have become a hot topic in electrochemical sensing and clinical testing [79].

Dan Tao, et al. developed a label-free electrochemical aptasensor for detection of Tau381 in human serum with detection limit of 0.70 picomolar [80]. To construct the sensing element, a specific aptamer against Tau381 was immobilized on a gold nanoparticle component of a nanocomposite comprised of carboxyl graphene/gold/thionin NPs (CG/TH/AuNPs) conjugated on a glassy-carbon electrode (GCE) surface. Thionin (TH) acts as a redox agent due to its electrochemical reversibility and rapid electron transfer [81]. After the interaction between aptamer and Tau381, TH generates an electrochemical signal which is measured with differential pulse voltammetry (DPV) (**Figure 5**)[80]. A novel approach to detect tau protein was introduced using a four-electrode electrochemical biosensor which operates based on antibody-antigen interaction at recognition surface. Four gold microband electrodes were assembled on a p-doped silicon substrate and coated with 3,3'-dithiobis sulfosuccinimidyl propionate (DTSSP) which is an organic cross linker polymer to create self-assemble monolayer (SAM). Specific antibody against tau protein (anti-tau) is conjugated to the covered microband electrodes via protein G molecules. With elevated concentration of tau protein, the capacitance and resistance of the sensor surface is also increased [82].

Several reaction sites and sufficient space for electrocatalytic active substances are provided by MWCNTs, considering the surface topological defects and large specific surface area. Low dissolving rate and high accumulation tendency are among MWCNTs drawbacks during clinical applications [83]. Nevertheless, carbon nanotubes are well dispersed in water, under influence of ultrasound, by another type of carbon nanomaterial, named Graphene Oxide (GO) [84]. Their synergistic effect is regarded as the reason for this process. Moreover, expansion of graphene

layer spacing and prevention of graphene sheets agglomeration are reached by MWCNTs [85]. Effectivity of the aforementioned components is highly improved when used synergistically as MWCNTs-rGO nanocomposites. For improving the low conductivity of GO, some of its oxygen-based groups are reduced thereby forming rGO (reduced graphene oxide) [86]. Additionally, rGO contributes to higher electrode modification potential of MWCNTs-rGO nanocomposite compared to MWCNTs-GO ones. Possessing a high adsorption rate, biocompatibility and film-forming potential, chitosan (CS) can immobilize the specific antibody and fix the modified materials on the electrode [86, 87]. In addition, AuNPs are commonly employed for biomolecules (antigen or antibody) signal amplifying-modifications due to their high physicochemical stability, conductivity and biocompatibility, along with large specific surface and facile synthesis [88, 89]. In a study, MWCNTs-rGO-CS nanocomposites were utilized to modify the gold electrode conductivity. Tau-441 protein was also modified with AuNPs in terms of signal amplification. 3-electrode system,$[Fe(CN)_6]^{3-}$ and $[Fe(CN)_6]^{4-}$, served as the redox probe provided the base of this study. DPV (differential pulse voltammetry) was performed to analyze the tau-441 protein and the specific antibody interaction, which was indicated by the sensing signal and controlled by the formation of tau-441 protein-specific antibody complex. . Complex formation and the electron transferring blockade led to signal alternations. The electrochemical biosensor response was linear at the 0.5–80 fM range (0.5, 1.5, 5, 10, 40, 80 fM) with LOD (limit of detection) of 0.46 fM, represented by DPV at 100–500 Mv range. 42 total number (14 test in each group) of serum analyses were successfully done by the biosensor for healthy samples, patients with mild cognitive impairment and dementia [90].

Detecting process of tau-441 protein needs to be highly sensitive, since BBB leaves only an insignificant amount of tau-441 protein in the blood. Another approach for electrochemical

biosensing of tau protein was implemented by immobilizing anti-tau on the surface of gold electrodes to provide a biorecognition element following tau441 interaction with anti-Tau molecules. Moreover, the electrochemical impedance spectroscopy has been employed to screen the interaction of antigen-antibody. A subsequent decline in charge-transfer resistance is noted due to the attachment of tau441 to Ab-Au[40].

4-3 Piezoelectric biosensors

Piezoelectric effect refers to the capability of generating an electric voltage following mechanical stress on specific materials. Also, reverse piezoelectric effect is when applying an external electric field to a piezoelectric material produces stress and oscillation[91]. The resonance frequency is inversely proportional to mass concentration of ligand bound to the receptor-coated surface. This correlation can provide an estimate of the ligand surface coverage and be useful in determining kinetic binding constants.

Primarily, a piezoelectric biosensor is constructed by immobilizing a receptor (antibody, nucleic acid, mimetic receptor, etc.) onto the surface of a piezoelectric quartz crystal (PQC) and monitoring the frequency changes due to the binding of specific ligands (antigen, nucleic acid or protein, etc.). The frequency of oscillations decreases on ligand binding and can be used to quantitatively estimate the ligand concentration, whereas the real-time monitoring of these changes can be used to calculate the kinetic binding constants [92]. Piezoelectric biosensors are reliable analytical tools; they represent a label-free detection of various microorganisms and biological molecules in addition to real-time information on the examined targets. In order to develop these group of devices, piezoelectric materials can be utilized as transducer and biologic molecules such as antibodies or nucleic acid sequences are employed to capture a desired target.

Nanoparticles in piezoelectric biosensors is also a promised method to further amplify the signal [93, 94]. Quartz crystal microbalance (QCM) has shown to be a potential material for developing sensor platforms with easy and cost-effective procedure that provides real time assays in short time. The QCM relies on a quartz crystal that undergoes different current-induced oscillations according to mass loading on the surface or changes of the viscosity or density of the media surrounding the sensor. The oscillation frequency is inversely proportional to interface phenomena. Hence, in these platforms, biochemical interactions can be directly displayed in real time and without any labels, allowing for simple detection of key biomarkers using consolidated chemistries, e.g., thiol chemistry coupled to amino coupling for receptor attachment, and several assay formats [95]. These biosensors are used for sensing various chemicals and biomolecules with high sensitivity. An oscillation at a particular frequency will be generated through applying a voltage on QCM which is the basis for the operation of piezoelectric biosensors [96]. Moreover, piezoelectric immunosensors are developed that use QCM for transduction and two specific monoclonal antibodies with different epitope recognition sites for capturing tau proteins in buffer and CSF sample. Primary monoclonal antibody is initially immobilized on the surface of QCM. Subsequently, to perform sandwich-based assay and enhance selectivity, secondary antibody is added to the test environment. Changes in frequency are observed after surface interactions [95]. In this platform, the primary mAb (mAb1) recognizes the middle domain (amino acids 189–195) of tau protein and is used as a capturing receptor for its direct detection by QCM measurements. Once bound to the analyte, it leaves the target protein free for further binding to a secondary mAb (mAb2) to improve the selectivity and detection limit of the bioassay. Finally, the analytical performances of the direct detection (via mAb1 recognition) and the sandwich-based assay (mAb1/tau/mAb2 recognition) were directly compared.

An original modification of the classical sandwich strategy was performed by substituting the mAb2 with tubulin, as an alternative natural recognition element [95]. High specificity and affinity of this recognition and its aimed stoichiometry play a major part in appropriate usage of tubulin as a secondary binder for tau protein [97-99]. In this regard, Ackmann et al. evaluated a K_D = 75 ± 30 nM and a stoichiometry of 0.20(defined by factor *n* = [tau]bound/[MT]) for tau protein in 5–500 nM , which is exactly where they focused on detecting tau in aCSF [99]. Additionally, sensor reuse of system may be effectively supervised by the future controlling of the in situ tubulin polymerization and its reversibility. For detecting the appropriate operating conditions, various buffers were employed to test tau–tubulin binding (mAb1 as primary receptor). At the beginning, tubulin was dissolved in the PB buffer, in which biomolecular interactions usually take place. To note, no secondary signal was reported due to tubulin dimers binding to tau (5 ± 2 Hz, *n* = 3); this finding was consistent in aCSF. Subsequently, it was revealed that PIPES, PEM and MES buffers containing Mg^{2+} salts and GTP (guanosine 5′-triphosphate) lead to tubulin polymerization [100-103]. It has been found that important unspecific binding in MES buffer when aCSF was spiked with 100 mg L^{-1} human serum albumin (HSA), corresponding to 42 ± 5 Hz (*n* = 3), likely due to an unspecific interaction between tubulin and HSA in solution. PEM however, was reported with an insignificant interference (2 ± 1 Hz, *n* = 3), and it was further elected for tau–tubulin interaction analyses [43]. At last, compared to the traditional secondary antibody-based approach, tau–tubulin has demonstrated a wider functional range coupled to a signal improvement,dose–response trend at lower tau concentration, than is usually investigated and closer to the physiological levels in the reference matrix for protein tau biomarker [43]. These findings expand the present limitations in

application of tubulin as an alternative receptor for tau protein ,considering its highly promising polymerization and reversible interaction with to this key hallmark AD [43].

5- Conclusion and future perspectives

Tau protein is shown to be a potential biomarker for early detection of AD. In recent years, several methods have been implemented to detect this protein. Biosensors are cost effective analytical devices for screening a desired target in a short time with high sensitivity and specificity. To date, multiple biosensors for detection of tau protein have been developed with distinct operating systems. Despite gains in detection of tau protein via biosensors, the standard detection limit is still a challenge as the accepted clinical concentration in body fluid samples is in picogram levels. Even so, application of nanomaterials-based biosensors could extend the detection scale values with high sensitivity and specificity. Various nano-based biosenosrs have been developed such as optical, electrochemical and piezoelectric biosensors. Different nanomaterials based on sensor type could be implemented as transducing part. Due to rising prevalence of Alzheimer's disease in recent years and lack of a definitive treatment, early detection is necessary to prevent its progression .In summary, biosensor-associated detection of AD biomarkers is evolving in parallel with integrating various nanomaterials, new chips and sensor devices for screening tau protein.

Declarations

Acknowledgements

Not applicable.

Funding

Not applicable.

Ethics approval and consent to participate

The current review article was settled in line to an original study that was approved by the local ethics committee of Tabriz University of Medical Science (IR.TBZMED.REC.1397.1042).

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Figures

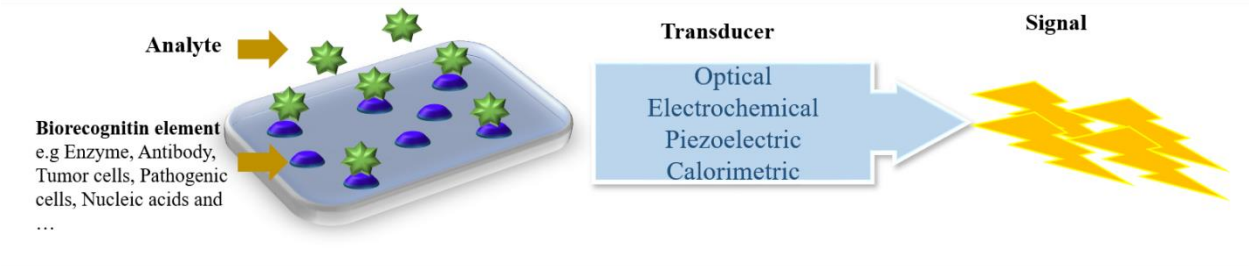

Figure 1: basic structure of a biosensor

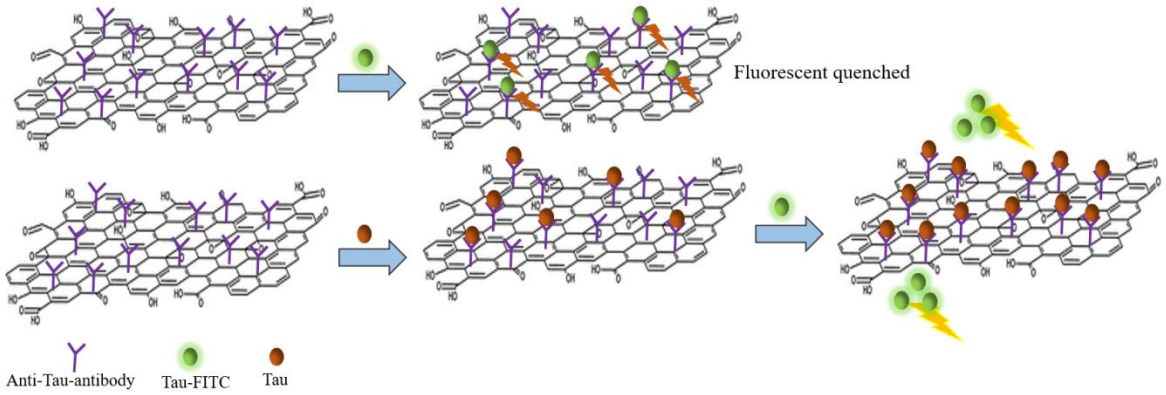

Figure 2: preparation of the fluorescent based biosensor for Tau detection

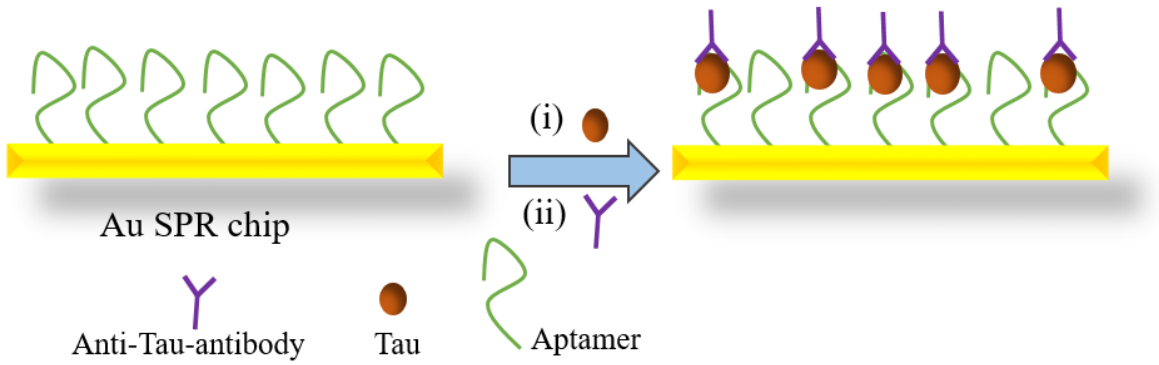

Figure 3: schematic overview of SPR-based method for Tau protein detection in plasma and buffer.

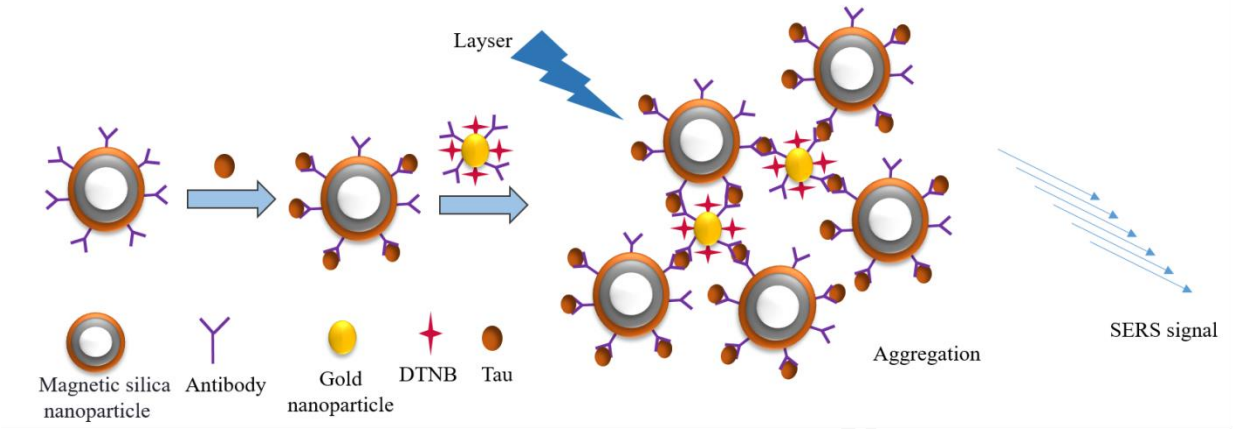

Figure 4: SERS based biosensing approach to detection of Tau protein

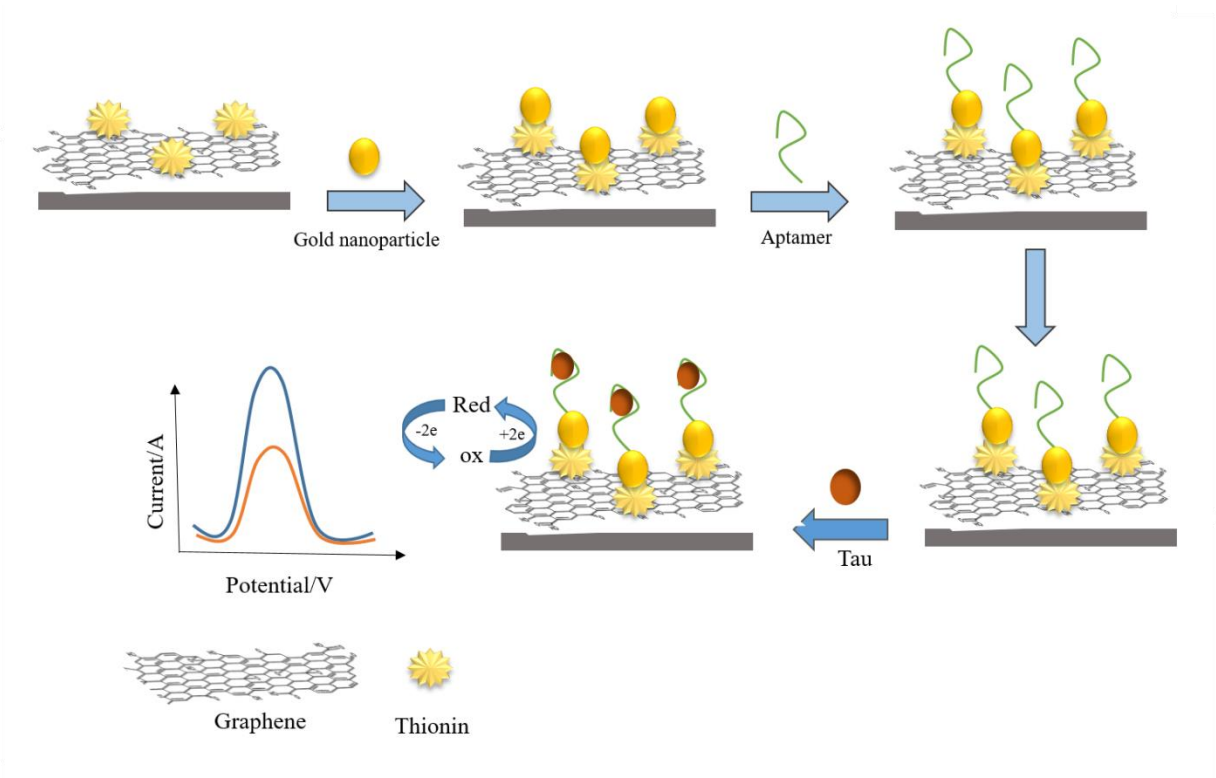

Figure 5: Electrochemical-based biosensor by differential pulse voltammetry evaluation of Tau381 level.

Table 1. Various biosensors for Tau detection

Biosensors	Examples	Limited detection	Advantage	Disadvantage	Biological sample	Type of Tau	Refs
Optical biosensors	-SPR biosensors -Immune-based SPR biosensor -Multimode optical fibers SPR biosensor -Fluorescent biosensors -Optical wave interferometry biosensors -SERS based biosensors	Femtomolar Picomolar	Direct, real-time; label-free detection; high specificity and sensitivity small size	Sensitive to sample matrix effects; sensor surface functionalization challenging; bulky optical equipment	Serum, aCSF, Plasma	Human tau, Tau12, Tau 381	[38, 39]
Electrochemical biosensors	-Biocatalytic biosensors -Affinity type biosensors -Four electrode electrochemical biosensor -Gold electrodes Electrochemical biosensors	Picomolar Nonomolar	Simplicity of using devices with high sensitivity; capable of operating with a very low sample concentration	Narrow or limited temperature range; limited shelf life; cross-sensitivity of other gases	Au surface, Serum, Equilibrium mixture	Tau441, Tau381, Tau410	[40-42]
Piezoelectric biosensors	-Immunosensing piezoelectric biosensors	Nanomolar	Reliable analytical tools; label-free detection; real-time data; small	Interference from atmospheric humidity; the difficulty in using them for the	Human Tau,	aCSF	[43]

and robust; and capable of giving a rapid response.	determination of material in solution