INTERNATIONAL JOURNAL OF
PHARMACEUTICAL AND HEALTHCARE INNOVATION
journal homepage: www.ijphi.com

Review Article

OPEN ACCESS

Advances in Alzheimer's disease: Unraveling Mechanisms and Harnessing Biosensors for Early Detection

Bhumika Chauhan*[1,2], Sweta Pundir[2], Divya Kumari[2] , Krishna Kumar[3], Arvind Kumar[1]

[1], Faculty of Pharmacy, IFTM University, Moradabad, 244001, Uttar Pradesh, India

[2] I.T.S College of Pharmacy, Ghaziabad, Uttar Pradesh 201206, India

[3] Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun 248007, Uttarakhand, India

Article Info

Article history:

Manuscript ID:

IJPHI0715212025
Received: 07-November -2024
Revised :15- January -2024
Accepted: 21- January 2025
Available online: January 2025

Keywords:
Alzheimer's disease, amyloid-beta, tau protein, biomarkers, biosensors, Disease monitoring

Corresponding Author:
chauhanbhumi9416@gmail.com

Abstract

One of the most severe neurodegenerative diseases, Alzheimer's disease is typified by steady cognitive deterioration, memory loss, and observable variation. Despite decades of research, the precise mechanisms underlying the pathophysiology of AD are still unknown. Recent advances have brought to light crucial molecular mechanisms underlying this illness, including synaptic dysfunction, amyloid-beta plaque accumulation, brain inflammation and tau protein hyperphosphorylation. These mechanisms are currently being described as probable biomarkers for ongoing illness progression monitoring and early detection. Laterally, cutting-edge biosensors technologies are revolutionizing how we monitor and analyze these biomarkers. Electrochemical, optical, and wearable biosensors are revolutionizing the detection of Alzheimer's disease (AD) by providing non-invasive, real-time, highly sensitive, and specific methods for measuring AD-related biomarkers. The development of this technology has the potential to greatly enhance early diagnosis, customize treatment regimens, and track the disease continually. By providing insight into the fundamental processes of AD, these biosensors are opening up new avenues for diagnosis and treatment, which will ultimately result in better patient outcomes.

Introduction

Alzheimer's disease (AD) is an irretrievable, obscure, and overwhelming neurodengerative disorder defined by progressive, persistent, recognizable failure and consciousness and the main cause of dementia [1-2]. This incurable illness influenced more than 50 million people in 2019 and this count is predicated to rise to 152 million by 2050 according to Alzheimer's disease International (ADI) and World health Organization (WHO) [3]. This situation stands as serious threat for the health system; therefore, AD get up to 604 billion dollars in damages in 2010. Despite the greatest danger factor for AD is age related, hereditary abnormalities can possibly cause AD in those below 65. Although it only makes up 4% of all cases, early-onset AD is uncommon [4]. Affected brains show two specific aberrant molecular structures as the disease progresses: 1) the generation of intraneuronal neurofibrially tangled of hyperphosphorylated tau protein, and 2). The extracellular collection of amyloid beta peptide (Aβ) in deposit over the neurons is recognized as senile plaques [5].

This study examines the new findings into the molecular mechanism of AD involving tau protein, hyperphosphorylation, amyloid-beta (Aβ) plaque aggregation, synaptic dysfunction, and neuroinflammation, have opened up current importance for the exploration for probable biomarkers and therapeutically goal. By offering unique, non-invasive, real time method for characterizing biomarkers and follow up of the progression of AD, recent biosensor technologies are also revolutionize the diagnosis and observation of AD [5-6].

Molecular Mechanism

Alzheimer's disease is a progressive neurodegenerative disease that involves a combination of factors. The exact cause of Alzheimer's disease is unknown, but a combination of genetic, environmental, and lifestyle factors likely plays a role [7]. Alzheimer's disease [AD] is a progressive neurodegenerative disorder that gradually erodes cognitive function, memory, and ultimately, the ability to carry out everyday tasks abnormal protein accumulation. While the exact cause of AD remains elusive, researchers have made significant strides in understanding the underlying mechanisms that contribute to its development [8].

In AD affected individual exhibited aberrant tau and beta-amyloid protein accumulations [9]. The precise mechanism of Alzheimer's disease is not entirely understood but generally characterized by the accumulation of two aberrant proteins in the brain: amyloid-beta plaques and tau neurofibrillary tangles. These proteins impair normal brain function, leading progressive cognitive deterioration and cell death. (10).

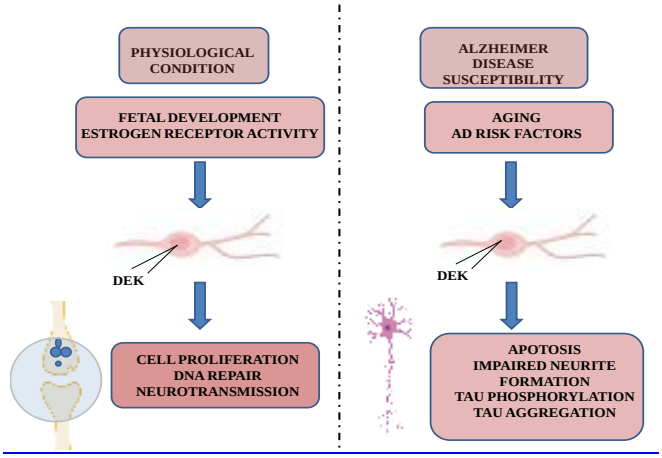

Fig:1Amyloidbeta plaques in Alzheimer's disease

It is not entirely clear that how Alzheimer's disease works, but the following steps are thought to be involved:

Amyloid-beta (Aβ) plaque formation:

- β is a fragment of a larger protein called amyloid precursor protein (APP) [11].
- In healthy individuals, the brain typically gets rid of Aβ.
- Aβ builds up between neurons in Alzheimer's disease and form plaques.
- Inflammation may arise due to disruption of neural connections brought on by these plaques [12].

Tau protein aggregation:

- Tau protein is normally involved in stabilizing microtubules, which are part of the neuron's transport system [13].
- In Alzheimer's disease, tau protein becomes hyperphosphorylated, causing it to misfold

and aggregate into neurofibrillary tangles [14].

- These tangles disrupt the neuron's transport system and lead to cell death [13-14].

Other factors that may contribute to Alzheimer's disease include [15]:

- **Inflammation:** Inflammation in the brain can damage neurons and contribute to the formation of plaques and tangles.
- **Oxidative stress:** Oxidative stress can damage cells and contribute to the progression of Alzheimer's disease.

- **Genetics:** The risk of Alzheimer's disease is enhanced due to several genes, including APOE ε4.
- **Lifestyle Factors:** The risk of AD may be influenced by variables such as diet, exercise, and cognitive stimulation.

Biosensors and its impact in AD diagnosis

Biosensors are analytical appliances that transcribe biological measures into quantitative signals. A diverse field containing sports [16-18], security [18-20] and the climate could be reconstituted by these appliances [21-22]. Because of their immediate, economical and unequivocal analyses, biosensor holds pledge as appliance to aid in the recognition of various illnesses in the field of medical [23-26]. On the basis of principles of detection, these are categorized and new advancements in wearable, optical and electrochemical sensors have the possibility to revolutionize clinical practice [27-29].

Neurochemical Biosensors: - Depression may occur due to an imbalance of some neurochemicals involving the stress hormones cortisol, serotonin, dopamine, and acetylcholine. A glucocorticoid hormone that is cortisol is elevated, which is linked to stress and mood disorders as well. Unconventional biosensors directly support the detection of neurochemical markers in sweat, sputum, and blood, contributing an unambiguous and non intrusive action to determine biochemical variations that signify depression [30-35].

Heart rate variability (HRV) sensor: - Variation in heart rate can also lead to changes in cognitive and emotional states. Depressed patients usually have intimacy of tachycardia or diminished heart rate variability (HRV), which is associated with disruption of the autonomic nervous system. Diminished HRV offers lesser parasympathetic nervous system activity, though tachycardia is generally associated with elevated sympathetic nervous system stimulation. These variations are precisely connected with anxiety and psychological stress [36].

A prominent non-invasive technique for observing and documenting heart electrical disruption is electrocardiograms (ECGs). To report cardiac electrical activity in twelve specific directions, conventional twelve-lead ECG systems utilize ten Ag-AgCl electrodes situated at particularized body sites. There are usually fewer electrodes used in wearable technology, which can be greatly partitioned into 2 types, namely dry electrodes and wet electrodes (gel electrodes) [37]. Using ordinary wearable technology, heart rate observing technologies are relatively advanced [38]. A smartwatches uses a photoplethysmorgraphy (PPG) sensor to record heart rate variability.

The arterial pulse waves generated by the heart's recurrent contraction and relaxation can be further detected to regulate heart rate. Stretchy and highly conformal patches are used to record insignificant mechanical vibration in the sternum in order to trace heart rate [39].

Thus, HRV sensors used in smartwatches, fitness trackers, or ECG devices regularly measure the fluctuation in the intervals between heartbeats, contributing significant facts about emotional states and autonomic function.

Sleep and Circadian monitoring:-

Several studies have verified that patients with depression usually have difficulty sleeping. Circadian rhythm troubles have been associated with depression [40]. The extent of the depression problem is further associated with the extent of circadian rhythm misalignment [31-42]. Polysomnography (PSG), which incorporates reports from EEG, electromyography (EMG), electrooculography (EOG), electrocardiography (ECG), respiration sensors, and blood oxygen saturation sensors, is the gold standard for equitably analyzing sleep aspects. These mixed findings are used to

build clinical analysis. Still, this approach constrains examining in a controlled laboratory atmosphere for 12 hours, which prepares assessments significantly bulky. Diverse wearable sleep monitoring systems have lately surfaced, commonly linking heart rate sensors [43] neuroelctrical signal electrodes [44], accelerometers [45] and audio-based breathing sensors 46]. Wang and colleagues, for instance, designed a ring -shaped wearable appliance that merges accelerometers, skin temperature sensors, heart rate sensors to measure stress levels and sensitive perception. A highest efficiency of 83.5 was accomplished by this system when joined with a backend IoT platform [47].

Electrodermal Activity (EDA) sensors: A depends on skin conductance and resistance fluctuating with sweat excretion. Several studies have concluded that depression is linked with electrodermal hypoactivity. Specifically, depressed people had lesser skin conductance (SCL) and the extent of skin conductance response (SCR) and elevated SCR inactivity as compared to healthy individuals [48-49].

Combined Wearable system

Physiological data containing heart rate variability, skin temperature and conductance, muscular movement, blood pressure, and brain electrical impulses have been exhibited to be vigorously connected with psychological stress in prior studies [50]. The progressive usage of medical accessories for monitoring body temperature, heart rate, breathing rate, arterial blood pressure, and oxygen saturation has been made easier in current years by progress in wearable biosensors and wireless transmission. Depression ancillary diagnosis and wireless, real-time, customized observations are now achievable.

Conclusion

One of the most severe neurodengerative diseases to diagnose. Alzheimer's disease has tangled molecular pathways and a demands potent initial detection method. Recent developments in understanding of the biology underlying AD have produced a number of curious biomarkers that can be used to track the progress of the illness. The detection of these biomarkers is being revolutionized at the same time by the advancement of biosensor technologies, which bring non-invasive, real-time, and extremely sensitive techniques for AD early detection and successful monitoring. Despite there are still concerns about growing and validating these technologies, biosensors have enormous promise to enhance diagnosed customized interest and observe the course of disease. With endless advancement and expanded integration into clinical practice, these technologies have the potential to incredibly strengthen Alzheimer's disease care.

Acknowledgments

The author would like to thank to Director, HRIT University, Ghaziabad and IFTM University, Moradabad for encouraging research work.

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

The authors do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required

References:

[1]. Sharallah OA, Poddar NK, Alwadan OA. Delineation of the Role of G6PD in Alzheimer's Disease and Potential Enhancement through Microfluidic and Nanoparticle Approaches. Ageing Research Reviews. 2024 Jun 29:102394.

[2]. Scheltens P, Blennow K, Breteler MM, De Strooper B, Frisoni GB, Salloway S, Van der Flier WM. Alzheimer's disease. The Lancet. 2016 Jul 30;388(10043):505-17.

[3]. Australia D, Baker S, Banerjee S. Alzheimer's Disease International World Alzheimer Report 2019: Attitudes to Dementia. Alzheimer's Disease International: London, UK. 2019.

[4]. Van Cauwenberghe C, Van Broeckhoven C, Sleegers K. The genetic landscape of Alzheimer disease: clinical implications and perspectives. Genetics in Medicine. 2016 May;18(5):421-30.

[5]. Huang Y, Mucke L. Alzheimer mechanisms and therapeutic strategies. Cell. 2012 Mar 16;148(6):1204-22.

[6]. Justino CI, Duarte AC, Rocha-Santos TA. Recent progress in biosensors for environmental monitoring: A review. Sensors. 2017 Dec 15;17(12):2918.

[7]. Williams, B. J., Eriksdotter-Jonhagen, M., & Granholm, A.-C. (2006). Nerve growth factor in treatment and pathogenesis of Alzheimer's disease. *Progress in Neurobiology*, *80*(3), 114–128. https://doi.org/10.1016/j.pneurobio.2006.09.001

[8]. *Alzheimer's disease fact sheet*. (n.d.). National Institute on Aging. Retrieved November 30, 2024, from https://www.nia.nih.gov/health/alzheimers-and-dementia/alzheimers-disease-fact-sheet

[9]. *Tau protein and Alzheimer's disease: What's the connection?* (n.d.). Brightfocus.org. Retrieved November 30, 2024, from https://www.brightfocus.org/alzheimers/article/tau-protein-and-alzheimers-disease-whats-connection

[10]. Gholami, A. (2023). Alzheimer's disease: The role of proteins in formation, mechanisms, and new therapeutic approaches. *Neuroscience Letters*, *817*(137532), 137532. https://doi.org/10.1016/j.neulet.2023.137532

[11]. Chen, G.-F., Xu, T.-H., Yan, Y., Zhou, Y.-R., Jiang, Y., Melcher, K., & Xu, H. E. (2017). Amyloid beta: structure, biology and structure-based therapeutic development. *Acta Pharmacologica Sinica*, *38*(9), 1205–1235. https://doi.org/10.1038/aps.2017.28

[12]. Hampel, H., Hardy, J., Blennow, K., Chen, C., Perry, G., Kim, S. H., Villemagne, V. L., Aisen, P., Vendruscolo, M., Iwatsubo, T., Masters, C. L., Cho, M., Lannfelt, L., Cummings, J. L., & Vergallo, A. (2021). The amyloid-β pathway in Alzheimer's disease. *Molecular Psychiatry*, *26*(10), 5481–5503. https://doi.org/10.1038/s41380-021-01249-0

[13]. Avila, J., Lucas, J. J., Pérez, M., & Hernández, F. (2004). Role of Tau Protein in Both Physiological and Pathological Conditions. *Physiological Reviews*, *84*(2), 361–384. https://doi.org/10.1152/physrev.00024.2003

[14]. Šimić, G., Babić Leko, M., Wray, S., Harrington, C., Delalle, I., Jovanov-Milošević, N., Bažadona, D., Buée, L., De Silva, R., Di Giovanni, G., Wischik, C., & Hof, P. (2016). Tau protein hyperphosphorylation and aggregation in Alzheimer's disease and other tauopathies, and possible neuroprotective strategies. *Biomolecules*, *6*(1), 6. https://doi.org/10.3390/biom6010006

[15]. Sun, Y.-Y., Wang, Z., & Huang, H.-C. (2023). Roles of ApoE4 on the pathogenesis in Alzheimer's disease and the potential therapeutic approaches. *Cellular and Molecular Neurobiology*, *43*(7), 3115–3136. https://doi.org/10.1007/s10571-023-01365-1

[16]. Rodriguez-Mozaz S, de Alda MJ, Marco MP, Barceló D. Biosensors for environmental monitoring: A global perspective. Talanta. 2005 Jan 30;65(2):291-7.

[17]. Amine A, Mohammadi H, Bourais I, Palleschi G. Enzyme inhibition-based biosensors for food safety and environmental monitoring. Biosensors and Bioelectronics. 2006 Feb 15;21(8):1405-23.

[18]. Campàs M, Prieto-Simón B, Marty JL. Biosensors to detect marine toxins: Assessing seafood safety. Talanta. 2007 May 15;72(3):884-95.

[19]. Vaisocherova H, Taylor AD, Jiang S, Hegnerová K, Vala M, Homola J, Yakes BJ, Deeds J, DeGrasse S. Surface plasmon resonance biosensor for determination of tetrodotoxin: Prevalidation study. Journal of AOAC International. 2011 Mar 1;94(2):596-604.
.

[20]. Garjonyte R, Yigzaw Y, Meskys R, Malinauskas A, Gorton L. Prussian Blue-and lactate oxidase-based

amperometric biosensor for lactic acid. Sensors and Actuators B: Chemical. 2001 Sep 25;79(1):33-8.

[21]. Nikolaus N, Strehlitz B. Amperometric lactate biosensors and their application in (sports) medicine, for life quality and wellbeing. Microchimica Acta. 2008 Jan;160:15-55.

[22]. Davis F, Higson SP. Carrier systems and biosensors for biomedical applications. InTissue Engineering Using Ceramics and Polymers 2014 Jan 1 (pp. 270-302). Woodhead Publishing.

[23]. Brazaca LC, Sampaio I, Zucolotto V, Janegitz BC. Applications of biosensors in Alzheimer's disease diagnosis. Talanta. 2020 Apr 1;210:120644.

[24]. Brazaca LC, Bramorski CB, Cancino-Bernardi J, da Silveira Cruz-Machado S, Markus RP, Janegitz BC, Zucolotto V. An antibody-based platform for melatonin quantification. Colloids and Surfaces B: biointerfaces. 2018 Nov 1;171:94-100.

[25]. Brazaca LC, Janegitz BC, Cancino-Bernardi J, Zucolotto V. Transmembrane Protein-Based Electrochemical Biosensor for Adiponectin Hormone Quantification. ChemElectroChem. 2016 Jun;3(6):1006-11.

[26]. Li M, Cushing SK, Wu N. Plasmon-enhanced optical sensors: a review. Analyst. 2015;140(2):386-406.

[27] Gautschi G, Gautschi G. Piezoelectric sensors. Springer Berlin Heidelberg; 2002..

[28]. L.C. Brazaca, Development of biosensors for assisting in the diagnosis of Alzheimer's disease, for the rapid quantification of melatonin and for the simple determination of the genetic trait of sickle cell anemia, Thesis presented to University of Sao Paulo, 2019.

[29]. Watson S, Young AH. Antidepressant effects of hydrocortisone. American Journal of Psychiatry. 2001 Sep 1;158(9):1536-a.

[30]. Steckler T, Holsboer F, Reul JM. Glucocorticoids and depression. Best Practice & Research Clinical Endocrinology & Metabolism. 1999 Dec 1;13(4):597-614.

[31]. Peterson RE, Wyngaarden JB, Guerra SL, Brodie BB, Bunim JJ. The physiological disposition and metabolic fate of hydrocortisone in man. The Journal of Clinical Investigation. 1955 Dec 1;34(12):1779-94.

[32]. Nestler EJ, Carlezon Jr WA. The mesolimbic dopamine reward circuit in depression. Biological psychiatry. 2006 Jun 15;59(12):1151-9.

[33]. Partridge JG, Apparsundaram S, Gerhardt GA, Ronesi J, Lovinger DM. Nicotinic acetylcholine receptors interact with dopamine in induction of striatal long-term depression. Journal of Neuroscience. 2002 Apr 1;22(7):2541-9.

[34]. Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. The serotonin theory of depression: a systematic umbrella review of the evidence. Molecular psychiatry. 2023 Aug;28(8):3243-56.

[35]. Evans CL, Ha Y, Saisch S, Ellison Z, Fombonne E. Tricyclic antidepressants in adolescent depression. A case report. European Child & Adolescent Psychiatry. 1998 Oct;7(3):166-71.

[36]. Roh T, Hong S, Yoo HJ. Wearable depression monitoring system with heart-rate variability. In2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society 2014 Aug 26 (pp. 562-565). IEEE.

[37]. Costantini S, Chiappini M, Malerba G, Dei C, Falivene A, Arlati S, Colombo V, Biffi E, Storm FA. Wrist-worn sensor validation for heart rate variability and electrodermal activity detection in a stressful driving environment. Sensors. 2023 Oct 12;23(20):8423.

[38]. Jo YT, Lee SW, Park S, Lee J. Association between heart rate variability metrics from a smartwatch and self-reported depression and anxiety symptoms: a four-week longitudinal study. Frontiers in Psychiatry. 2024 May 31;15:1371946.

[39]. Zavanelli N, Lee SH, Guess M, Yeo WH. Continuous real-time assessment of acute cognitive stress from cardiac mechanical signals captured by a skin-like patch. Biosensors and Bioelectronics. 2024 Mar 15;248:115983.

[40]. Zaki NF, Spence DW, BaHammam AS, Pandi-Perumal SR, Cardinali DP, Brown GM. Chronobiological theories of mood disorder. European archives of psychiatry and clinical neuroscience. 2018 Mar;268:107-18..

[41]. Edgar N, McClung CA. Major depressive disorder: a loss of circadian synchrony?. Bioessays. 2013 Nov;35(11):940-4.
[42]. Hasler BP, Buysse DJ, Kupfer DJ, Germain A. Phase relationships between core body temperature, melatonin, and sleep are associated with depression severity: further evidence for circadian misalignment in non-seasonal depression. Psychiatry research. 2010 Jun 30;178(1):205-7.
[43]. Parak J, Tarniceriu A, Renevey P, Bertschi M, Delgado-Gonzalo R, Korhonen I. Evaluation of the beat-to-beat detection accuracy of PulseOn wearable optical heart rate monitor. In2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) 2015 Aug 25 (pp. 8099-8102). IEEE.
[44]. Kwon S, Kim HS, Kwon K, Kim H, Kim YS, Lee SH, Kwon YT, Jeong JW, Trotti LM, Duarte A, Yeo WH. At-home wireless sleep monitoring patches for the clinical assessment of sleep quality and sleep apnea. Science Advances. 2023 May 24;9(21):eadg9671.
[45]. Migliorini M, Mendez MO, Bianchi AM. Study of heart rate variability in bipolar disorder: linear and non-linear parameters during sleep. Frontiers in neuroengineering. 2012 Jan 10;4:22.
[46]. Mantua J, Gravel N, Spencer RM. Reliability of sleep measures from four personal health monitoring devices compared to research-based actigraphy and polysomnography. Sensors. 2016 May 5;16(5):646..
[47]. Mahmud MS, Fang H, Wang H. An integrated wearable sensor for unobtrusive continuous measurement of autonomic nervous system. IEEE Internet of Things Journal. 2018 Aug 31;6(1):1104-13.
[48]. Sarchiapone M, Gramaglia C, Iosue M, Carli V, Mandelli L, Serretti A, Marangon D, Zeppegno P. The association between electrodermal activity (EDA), depression and suicidal behaviour: A systematic review and narrative synthesis. BMC psychiatry. 2018 Dec;18:1-27.
[49]. Rykov YG, Ng KP, Patterson MD, Gangwar BA, Kandiah N. Predicting the severity of mood and neuropsychiatric symptoms from digital biomarkers using wearable physiological data and deep learning. Computers in Biology and Medicine. 2024 Sep 1;180:108959.
[50]. Ertin E, Stohs N, Kumar S, Raij A, Al'Absi M, Shah S. AutoSense: unobtrusively wearable sensor suite for inferring the onset, causality, and consequences of stress in the field. InProceedings of the 9th ACM conference on embedded networked sensor systems 2011 Nov 1 (pp. 274-287).