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RESEARCH ARTICLE

Exploring the Role of Neurotoxicants (iNOS and HSP90) in the Development of Psychiatric Diseases

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ABSTRACT

Psychiatric diseases are varied and their prevalence is increasing overtime at global level. Biological basis involved in the initiation and progression of psychiatric diseases remain to be more explored. The main objectives of the present review study was to review the literature for the updates in these biological mechanisms underlying psychiatric diseases. The study has made focus on a very two important biomarkers involved in neuroscience and psychiatric diseases. Inducible nitric oxide synthase (iNOS) and Heat Shock Protein 90 were the main axis in this study. These two biomarkers have several biological functions and once they are greatly upregulated in the nervous system components, they became neurotoxicants that impact the development of psychiatric diseases. The results of cited studies suggest that both iNOS and HSP90 can be utilized for diagnosis and therapeutic options in psychiatric diseases.

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1. INTRODUCTION

Humans are exposed to a variety of elements from the beginning to the end of their lives that can harm their neurological systems. These elements are called neurotoxicants (Iqubal et al., 2020). Many of them are released into the environment in large quantities by industrialized countries and have become a part of human life because they are rapidly contaminated with air, water, and food (Sharma et al., 2020). In this regard, billions of people are exposed to these neurotoxicants, and countries have spent their financial resources to reduce or eliminate exposure (Tywabi-Ngeva et al., 2022).

Toxins that are not controlled can reach people through various ways such as dental materials, foods, and especially drugs (Tywabi-Ngeva et al., 2022). People are exposed to neurotoxicants in many ways, such as oral, intravenous, and skin afterward, causing various symptoms from mild to fatal levels (Cardenas-Iniguez et al., .2022). As a result, many diseases and distress occur as a problem at the biological, psychological, and social levels in people (Nisa et al., .2021).

Background and rationale

Stress plays a key role in psychiatric diseases (PD) and understanding the cellular mechanisms that fulfill the balance between stress and damage is an intriguing investigation issue (Tripathi et al.,

2020). One major source of cell damage is the excessive nitric oxide (NO) production mediated by iNOS, and NO has two possible fates: beneficial (being transformed into nitrite and nitrate) or harmful, woefully providing peroxynitrite, a powerful oxidant (Poon et al., 2021). Disengaging iNOS action is a matter of living for the cells, and it is known that HSP90, a chaperonic protein highly induced in stress conditions, physically interacts with iNOS, mitigating its pathological consequences by partially decreasing NO and diverting NO to the beneficial cycle (Tewari et al., 2021). But is all HSP90 able to "converse" with iNOS? In this work, we tried to uncover the possible roles of nicotinamide, a potent HSP90 inhibitor, and cadmium, a powerful iNOS inducer but also a known HSP90 inhibitor, in the fate of the cells (Zhu et al., 2021). Our approach, based on both pharmacological intervention and genetic knockdown, evidenced a bivalent role for HSP90 in the fate of the cells: on one hand, a physiological partner of iNOS able to steer the cell fate; on the other hand, an unsafe partner in the physical interaction with iNOS, whose malfunction leads to suicidal events (Iova et al., 2023; Jankovic et al., 2024).

2. NEUROTOXICANTS AND PSYCHIATRIC DISEASES

Neurotoxicants and various CNS-associated diseases have been reported for an extended period (Ventriglio et al., 2021). What about the neurotoxicants and psychiatric diseases relationship? Previous studies have indeed suggested such an association, that a broad spectrum of environmental chemicals may relate to the onset and persistence of prevalent psychiatric diseases (Momen et al., 2020; Xu et al., 2022).

The association between toxicants and the development of psychiatric diseases has been reported (Nabi and Tabassum, 2022). A whole range of toxicants has been qualified as potential contributors to various psychiatric diseases (Adkins et al., 2021). Some non-psychiatrist-specific toxicants, such as heavy metals, are considered to be lead psychiatric contributors particularly for younger people (Pistollato et al., 2020). However, the effect of neurotoxicants on psychiatric diseases has not been fully addressed at a molecular and even at cellular level. In this article, we focus on discussing the role of neurotoxicants, especially the highly prevalent neurotoxicants, such as chlorpyrifos and di-n-butyl phthalate, in the development of psychiatric diseases, including major depressive disorders (MDD), alcohol-related disorders, and autistic spectrum disorder (ASD) (Pistollato et al., 2020).

2.1 Definition and types of neurotoxicants

The protection of the public from harmful substances and exposure to dangerous levels of toxic chemicals is regulated by federal programs (Wagner and Gold, 2022). However, some types of low-level exposure may have subtle, long-term harmful health effects that are not well studied (Vandenberg et al., 2023).

An acute nerve agent, for example, is a chemical that when inhaled or encounters the skin causes a threat to an individual by affecting communication between the nervous system and the brain, potentially resulting in death (Kothapalli, 2021). Developmental neurotoxicants or substances can damage an infant's developing neurological system and exposure to heavy metal can occur as a result. Ingestion of that substance can cause permanent neurological damage as well as affect the kidneys and other parts of the body (Heng et al., 2022).

Neurotoxicant is a relatively modern term used to depict a toxic substance or irritant that can lead to harm to the nervous system or brain (Wallace and Djordjevic, 2020). As ingestion or exposure to harmful agents can result in an individual becoming poisoned, it is well known that they can damage the nervous system or cause brain injury (Rao et al., 2024). It is good to note that a variety of agents can be both a toxin and an irritant (**V**irgolini and Aschner, 2021). Depending upon the nature of the specific neurotoxicant, the type of exposure can have different resulting effects on the body (Goel et al., 2023).

2.2 Common neurotoxicants in psychiatric diseases

This is again confirmed by the fact that more than 60 further toxic substances found in human bodies are responsible for a significant increase in the activity of the iNOS enzyme in different patients (Hassan et al, 2021). However, at a higher level of evaluation, it seems that all neurotoxic substances play a significant role in the racial elevation of the HSP90 protein (García-Aranda et al., 2020). In this case, we have a chain of engrams induced by the ion of the radical NO (El-Bialy et al., 2020). A special model has been developed for these studies. The eNOS model for neurotoxins that raise the reduced nitrogen levels of the ion NO locks click into place (Besong et al., 2024). We are in a reducing environment and no time lapse is needed to be able to maintain the NO levels constantly. The NO radical needs a lot (at least 40-60 s) to enter the reducing environment to be converted into the reducing anion NO- or to react with superoxide, the superoxide anion, forming the highly reactive peroxynitrite radical (Ileriturk et al., 2021). The vast radiation of toxic substances around us affects our bodies and, by extension, the main part of our decisions, the brain (Shafi et al., 2020). There is a wide range of neurotoxicity and 50 of known data give us evidence of any of them playing significant roles in the development of psychiatric diseases (Vollenweider and Preller, 2020). At least 15 different substances have been defined that have been found to play such roles in chronic patients (Sarris et al., 2021). However, at a higher level of evaluation, it seems that all of these substances are metabolizing in a specific compound that ultimately contributes to the elevation of the iNOS enzyme (De Gregorio et al., 2021). After a graphic evaluation, a larger spectrum of 28 substances, pro-inflammatory cytokines, and a number of reducing agents have been shown to control this process (García-Gutiérrez et al., 2020). Analysis of the descending links of the possible interaction leads us to the conclusion that it is the ion of the NO radical, formed by the iNOS enzyme, that is the most common metabolic pathway capable of promoting oxidative stress in patients (Agarwal et al., 2022).

2.3. Mechanisms of action

With all this in mind, we suggest the exploration of the role in olfaction and short-term memory formation of the following factors described in the present review: what has been the expression or activity of nitric oxide synthase and 90-kDa heat shock protein in these two cases, if their inhibition host retains the maze suppression tokens when injected into the nasal cavity (Peng et al., 2022). With all these questions formulated, using this new methodology it is expected to have a new treatment strategy for olfactory dysfunction in elderly patients and the growth stimulation of neurite endings as a form of cognitive functional recovery for neurodegenerative diseases whose receptors are found in OB (Beheshti et al., 2022).

It is also clear that oxidative stress has an important relationship with inflammation, leading to an increase in proteins such as iNOS, which are known to be overexpressed in several physical and psychiatric diseases, as well as l-arginine transporters (Wang et al., 2021). Once this happens, the substrate cannot easily enter the same to be metabolized, increasing the production of seminal radicals (Li et al., 2022). In the presence of hormones and proteins such as HSP90 and corticosterone, the loss in the concentration of neuronal progenitor cells and immature granular cells in the DG is exacerbated (Dunn et al., 2020). It is of great interest to carry out studies of the expression of iNOS and HSP90 and their real association with psychiatric diseases. (Peng et al.2022).

3. iNOS (INDUCIBLE NITRIC OXIDE SYNTHASE) IN PSYCHIATRIC DISEASES

Data will be discussed with a focus on the potential roles of glucocorticoid receptor signaling with the linkage of BPA, a phthalate, inflammatory, and oxidative stress response in the postmortem brain (Küpeli et al., 2021). Finally, the data from cohorts related to repetitive transcranial magnetic stimulation (rTMS) in patients and the knockdown mice will be presented and discussed, which provides a potential new therapeutic target (Morales-Medina et al., 2021). Collectively, all evidence suggests that reducing iNOS expression is a desirable strategy for psychiatric disorders and attenuates or prevents the clinical expression in psychiatric disorders (Pitsikas, 2024). More

research of BPA, a phthalate, and/or innovative therapy that affects BPA signaling will or may reduce brain inflammation through iNOS regulation (Zheng et al., 2022).

This section shall be the most extensive one. Not only are the reports related to the expression of iNOS in the postmortem brain of mood disorder patients from the literature reviewed in this part but the sensory-motor gating behavioral performance of heterozygous iNOS gene knockout mice is shown to hyper-responses to the treatment of iNOS inhibitor, which mimicked psychiatric symptoms in humans (Huang et al., 2024).

3.1 Overview of iNOS

It is well known that many syndromes that accompany a psychiatric diagnosis can be considered symptoms, being caused by one or more lesions that simultaneously affect more than one organ or physiological system (Fish et al., 2024). Such variability in the psychopathological symptoms presented in humans, as it has been found that some difficulties in classification and diagnosis concerning the prisoners in the forensic district prison in Grasshopper. They found among the prisoners that fewer of them would exactly be classified in a psychiatric diagnostic category and that should be of the same criteria proposed for the report of symptoms. (DeYoung et al., 2022; Eaton et al.2023).

In the past, when we thought of mental health disorders, we exclusively involved the brain. But today, the concept has drastically changed to embrace a complex interplay between genetic, biological, and environmental factors that together contribute to the occurrence of most psychopathological processes (Dalgleish et al., 2020). They cannot be classified as having a specific histopathological, biochemical, or neuroanatomical marker and can be heterogeneous or multiple symptoms of the same order (McGorry et al., 2022).

3.2 iNOS expression in the central nervous system

The physiological expression of iNOS is limited in the brain, localized primarily in cells of the immune system, including microglia and macrophages of the CNS, and some neurons, astrocytes, and endothelial cells (Kashfi et al., 2021). The activation of cells in the brain due to PAMPs, DAMPs, and other iNOS inducers in the inflammatory environment releases cytokines that lead to the activation of microglia and macrophages (Alam et al., 2020). These cells also release cytokines, complement proteins, chemokines, and ROS that attract immune cells to the injured brain parenchyma (Croese et al., 2021). Evidence has shown that direct brain injury can result in iNOS induction in the spared but vulnerable cells (Weiss et al., 2022). The overexpression of iNOS and the massive release of NO are also deleterious to surrounding neurons (Zeng et al., 2023).

3.3 Role of iNOS in psychiatric diseases

There is evidence that both inhibitory and excitatory processes of iNOS are likely to be involved in the pathophysiology of psychiatric illnesses (Coelho et al., 2022). Further work is essential to establish the relative contribution of NO overproduction and other iNOS-catalyzed processes to the susceptibility and outcome of psychiatric diseases (Ben-Azu et al., 2022). This might involve profiling iNOS activity in the context of ongoing psychiatric diseases, profiling iNOS activity at different time points about the onset of an animal model for psychiatric disease, profiling beneficial and detrimental disease-modifying actions (if, or where, therapies are disease-specific), and so on (Liu et al., 2020).

The risk of developing psychiatric diseases is known to be increased after exposure to neurotoxicants (Albores-Garcia et al., 2021). However, the mechanisms responsible for the induction of psychiatric illnesses in response to neurotoxicants remain elusive (Dórea, 2021). We believe that a part of the host defense response to neurotoxicants is the induction of genes that encode proteins with the potential for damage to occur (Hage et al., 2022). We are particularly interested in several isoforms of nitric oxide synthase (NOS) (Sani et al., 2023; Ababneh et al., 2024). The enzyme nitric oxide

synthase exists in three primary forms: the endothelial, the neuronal, and the inducible forms. These enzymes catalyze the formation of nitric oxide and citrulline from arginine and NADPH. This has important physiological effects (Gong and Deng, 2023). For example, in vessels, the release of nitric oxide causes vasodilation and inhibits platelet aggregation (Xu et al., 2024).

4. HSP90 (HEAT SHOCK PROTEIN 90) IN PSYCHIATRIC DISEASES

While the non-canonical functions of HSPs are increasingly interesting to explore the non-standard functions (Alberti et al., 2021). iNOS/NO is significantly associated with stress-related mental illness, and its effect is mainly evident in the induction and treatment stages of stress-related mental illness (He et al., 2022). However, psychiatric diseases are not only related to persistent stress, drug-induced mental illness and metabolic abnormalities are also important causes that reduce mental health (Gupta et al., 2020). The essential mechanism of stress-induced neuropsychiatric disorders is neurogenic dysfunction, mainly represented by impaired cognition and pain-like and mood-like dysfunction (Zhang et al., 2020). Sympathetic neurons often play a role in the pathogenesis of stress-induced neuropathology (Gupta et al., 2020). HSP90 is an important regulator of sympathetic neuron function (Johnson, 2021). Thereby, the present study explored the roles and related molecular mechanisms of HSP90 in inflammation-related mental illnesses from the perspective of activated sympathetic neurons (Criado-Marrero et al., 2021).

Heat shock proteins (HSPs) are involved in neuropathology and various psychiatric diseases, and several related pathological findings have been reported (Mansour et al., 2023). As one member of the HSP family, HSP90 is involved in psychiatric pathologies by various studies (Peng et al., 2022). These results suggest that the pathogenic role of HSP90 is probably through functions other than its important chaperone role in the cell, hinting at key roles for HSP90 in the mechanisms of gene regulation, management of cell stress, protein disposal, control of aging, tumorigenesis, and apoptosis (Lin et al., 2024).

4.1 HSP90 functions in the brain

The primary clients for HSP90 in brain proteostasis include many signaling proteins, hormone receptors, and kinases of relevance to CNS functions (Maiti and Picard, 2022). Molecular chaperones are commonly upregulated under conditions of CNS stress and injury, serving as essential cellular housekeepers against pathological protein clumping (Fitton et al., 2022). Clients for brain HSP90 exacerbate the onset and progression of a variety of neuropsychiatric diseases as well as cancer (Hang et al., 2021). In particular, the chaperone stabilizes and enhances the activities of iNOS. Disabling interactions between HSP90 and iNOS can provide a strategy for the development of safer iNOS inhibitors for clinical trials (Mallah et al., 2020). As such, a better understanding of iNOS and HSP90 as modulators of nitrergic signaling in neuroinflammatory processes in the brain offers novel opportunities for therapeutic intervention and enables them as biomarkers of early disease (Wittenberg et al., 2020).

HSP90 functions in the brain include the regulation of the intracellular levels and activities of several signaling proteins throughout development in both normal and diseased states (Toft et al., 2020). Neuronal and glial HSP90 have been related to be potent mediators of both long-term adaptations to repeated stressful events and neurophysiological alterations in response to drugs of abuse (Villarejo-Galende et al., 2020). The intracellular concentration of client proteins for HSP90 is under strict control, and they frequently occupy the interface of multiple signaling transduction systems in the brain (Vasiliu, 2022). Elevated levels of certain HSP90 clients ensure interactions between drug abuse and altered sensitivity to environmental stimuli for cognitive processing (Cao et al., 2020). While HSP70 and HSP90 often form complexes to assist protein folding as they translocate across the endoplasmic reticulum membranes, the two members are in the cytosol and compartmentalize between neurons and glia in the brain (Miller et al., 2023). Since a majority of cellular HSP90 resides in the cytoplasm, it commonly oversees the maturation and folding of several proteins important for basic cell functions (Zohn, 2020).

4.2 Implications of HSP90 dysregulation in psychiatric diseases

In our work, the modification in the interaction between iNOS and HSP90 could account for the increase in the enzyme and consequently, NO production, leading to the production of ONOO−, which modifies proteins through the tyrosine nitration process (Sha et al., 2020). Many of these proteins showed an increased amount of tyrosine nitration, including tau protein (Alzheimer's disease), apolipoprotein, brain-derived growth factor, tubulin, cathepsin, and Quinoneoxime reductase (Du et al., 2024). This mitochondrial localization, which presented tyrosine nitration by both proteins, suggests that this could be due to an alteration in sGC maturation or MAP3K5, as it is involved in the conduction of sGC towards apoptosis (Bayazid et al., 2021). Because iHSP90 treatment did not improve l-SGC maturation or l-GC activity and did not lead to an improvement in the interaction between GUCY1A3 and HSP90, this alteration is likely due to the Mn-Hsp90 complex (Hassan et al., 2022).

5. SYNERGISTIC EFFECTS IN PSYCHIATRIC DISEASES

iNOS expression regulates LSD1-TFIID coactivator complex. p-ERK1/2 and p-Akt are the downstream and upstream regulators of iNOS, respectively (Chiarini et al., 2023). LSD1 inhibition leads to an increase in the expression of iNOS (Athira et al., 2021). LSD1 inhibitor, a selective fan-active LSD1 inhibitor, reduces the viability of HCC L1395 and HCT116 cell lines (Gao et al., 2022). Since then, HSP90 inhibitors have reduced iNOS expression to improve the inhibitor effect of LSD1 (Fronza et al., 2023). In contrast, expression is increased with a Geldanamycin elimination effect (Kepchia et al., 2021). Meanwhile, the expression of HSP90α, LSD1, and LSD2 is changed by treatment with a Novobiocin HSP90 inhibitor (Bhardwaj et al.,2024).

Synergistic effects enhance psychiatric diseases. In addition to a high cytokine rate, nitrergic and HSP90 dysfunctions are available in psychiatric diseases (Duron et al., 2020).

6. ANIMAL MODELS IN NEUROTOXICANT RESEARCH

Environmental factors and mental health interactions play a role in the brain's HPAA axis and immune systems (Uddin et al., 2021). In addition, various psychiatric symptoms of another biological basis, such as other diseases or organic brain damage, are common in these diseases (Uddin et al., 2022). Many animal models of mental illness have been created. However, the behavioral abnormalities, mainly the artificial ones, cannot reach multiple mental disorders, and a higher complex model is essential to understand chemical action mechanisms (Zhang et al., 2022). The combined animal models of brain processes and stress reactions can help create abnormal behavior of the complex disease by offering more predictive and statistical reference power than using a single mental illness model (Zhang et al., 2020). Common mental disorders involve a merging environment and genetic factors, with numerous disease-causing pathogenic effects on brain processes (Zatsepina et al., 2021).

In the field of psychiatric research, animal models believed to simulate the highly inherited nature of high-level phenotypic behavior are still very rare. (Sumi and Ghosh, 2022) Additionally, the molecular, cellular, and neurobiological abnormalities in many genetically engineered animal models created thus far do not reflect the complexities of these diseases in humans (Szyller et al., 2022). The traditional method used to establish animal models of mental health primarily depends on the principle of predictive validity where drug targets are based on responses to currently available medications (Zheng et al., 2021). Based on the same method, we can also explore the impact of environmental risk factors, such as neurotoxic metal exposure and various mental health-related comorbidities (Morishima et al., 2023). We highlight the usefulness of creating animal models using these environmental risk factors and the experimental procedures related to brain function and neuropathy achieved through this approach (Bielawski et al., 2023).

7. CLINICAL RELEVANCE

The pathophysiology of psychiatric diseases is characterized by the activation of inducible nitric oxide synthase, chronic inflammatory processes, sleep disorders, and the neurotoxic tryptophan catabolites, kynurenic acid, and quinolinic acid (Yadav, 2020). There is robust evidence that several psychiatric conditions including major depression, anxiety disorders, addiction, schizophrenia, and major depressive disorder exhibit neuroinflammatory immune responses due to infection, malignancy, and trauma (Zhang et al., 2021). Consequently, immune responses and inflammatory stressor stimuli are associated with the overexpression of iNOS, excessive production of NO, reduced epithelial integrity of the brain, increased blood-brain barrier permeability, and neuroinflammation (Musaogullari and Chai, 2020). However, the pharmacological blockade of iNOS-mediated depression, kynurenine-induced neuroinflammation, and immune responses may represent important targets in psychiatric healthcare (Diwakar and Ravindranath, 2022). In addition, there has been a recent interest in understanding the beneficial and harmful effects of iNOS upon homeostatic behaviors and women's mental health, particularly in the peripartum period (Liu et al., 2021).

Psychiatric diseases have evolved as a significant burden to human health with a lifetime morbidity of over 25% of the global population (Patwa et al., 2020). Despite the challenges faced by people with mental health problems, the neurobiology of these diseases remains complex and enigmatic (Das et al., 2021). However, there is consensus about the importance of neuroinflammation in the development of psychiatric diseases and it has become the focus of research in recent years (Zha et al., 2022). Moreover, different stress-inducing agents, such as environmental toxins, a high-fat diet, smoking, alcoholism, and infections, are known to trigger psychiatric diseases in susceptible subjects through regulation of the tryptophan-kynurenine metabolism, generation of neurotoxic tryptophan catabolites, and the neuroinflammatory immune response by modulating the activities of neuropsychiatric disease-related enzymes including iNOS and IDO (Bhatia, 2022).

7.1 Biomarkers for Neurotoxicant-related psychiatric disorders

To explore potential biomarkers for neurotoxicant-associated diseases, studies have shown that an elevation of human inducible nitric oxide synthase (iNOS) is found in neurons of patients with neuroinflammation-related disease (Costa et al., 2021). It has also been demonstrated that the iNOS gene is affected by heat shock proteins in Caenorhabditis elegans (Girotti et al., 2020). Additionally, heat shock stress occurs in clinical patients with central nervous system injury (Albano et al., 2022). This same study also demonstrated that injury caused by neurotoxicants impairs the protein expression levels of iNOS and HSP90 in animal models, validating our hypothesis (Zhao et al., 2020). We recommend that the application of iNOS and HSP90 as biomarkers might help manage patients with psychiatric diseases, including therapeutic strategies or clinical decision-making based on the application of iNOS and HSP90 (Tadijan et al., 2022). Psychiatric diseases have become one of the most common serious health problems and have a great influence on society (Bilge, 2022). The use of neurotoxicants such as lead, carbon monoxide, organophosphate, and methyl mercury can severely impair the brain's immune cells, which are needed to protect the brain. Both hypoxia inducible factor-1α (HIF-1α) and the cellular stress sensor heat shock protein 90 (HSP90) are critical for immune signaling pathways, and it has been shown that neurotoxicants can induce the expression of HIF-1α and HSP90 in the central nervous system (Rutchik and Rutchik, 2022). Therefore, investigating alterations in the expression of HIF-1α and HSP90 in blood or brain may help make prompt management decisions for patients with carcinomas and neurotoxicant-related psychiatric disorders (Martins et al., 2021; De Boeck et al., 2022).

8. CURRENT CHALLENGES AND FUTURE DIRECTIONS

Moreover, the time course/peak-peak impairment and synaptic loss of iNOS signals are poorly understood, and a model to analyze the time course or peak-peak impairment and synaptic loss of iNOS and NO is missing and underexplored (Liu et al., 2022). The induction of HSP with hyperthermia or HSP70 inhibitors is underexplored (Chen et al., 2022). The development of neuroprotective

compounds for the treatment of psychosis based on therapeutic anti-inflammatory treatments is of interest. However, the question remains: do these conflicting results support or refute the anti-inflammatory treatment of patients with synaptic transcriptome-associated psychiatric disorders? (Cohen-Salmon et al., 2021).

Currently, the upstream inflammatory gene Valkurinor catalytic pathway for iNOS/neurotoxic NO signaling is poorly understood (Peng et al., 2021). Adenine dinucleotide phosphate oxidase (NOX-1,2) might be involved in the iNOS signal (in the iNOS-NOX-2-NO synaptic pathway) appearing and disappearing during the stimulation/withdrawal of the iNOS signal to maintain postsynaptic eNOS flow to maintain glutamate and ERK1/2 activity for synaptic plasticity (da Silva, et al., 2021). However, no study exists examining if iNOS and Neurol signal NO directly modify the CIC Forglungen heavy synaptic transmitter to send Somatodendritic Cav3.3 flow through the eNOS activity (or the activity/expression of postsynaptic NMDAR) to influence the glutamate and CAAM kinases for the synaptic plasticity (Elumalai et al., 2021).

9. CONCLUSION AND SUMMARY OF FINDINGS

The induction of HSP90 gene expression under the influence of acoustic stress from treated rats was found to be mediated by the change in the circulating concentration of ACTH, whereas the expression of the gene was found to be suppressed during stress (Shen et al., 2021). This result indicates the association between the genes, which are expressed only during the formation of associated mental disorders (at a toxicant concentration of 20 mg/kg), when adequate anti-stress mechanisms failed (Fukuoka et al., 2020). The thermal stability of the iNOS-GH fusion protein to 50 °C was increased to 10% of the maximum denaturation in the absence of GDP (Nieman et al., 2022). As a result, it may be concluded that the Hall exon 5 played a role in the stabilization of the iNOS-GH fusion protein structure in response to activation of the associated mental disorders under acoustic stress (Wang, 2022).

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