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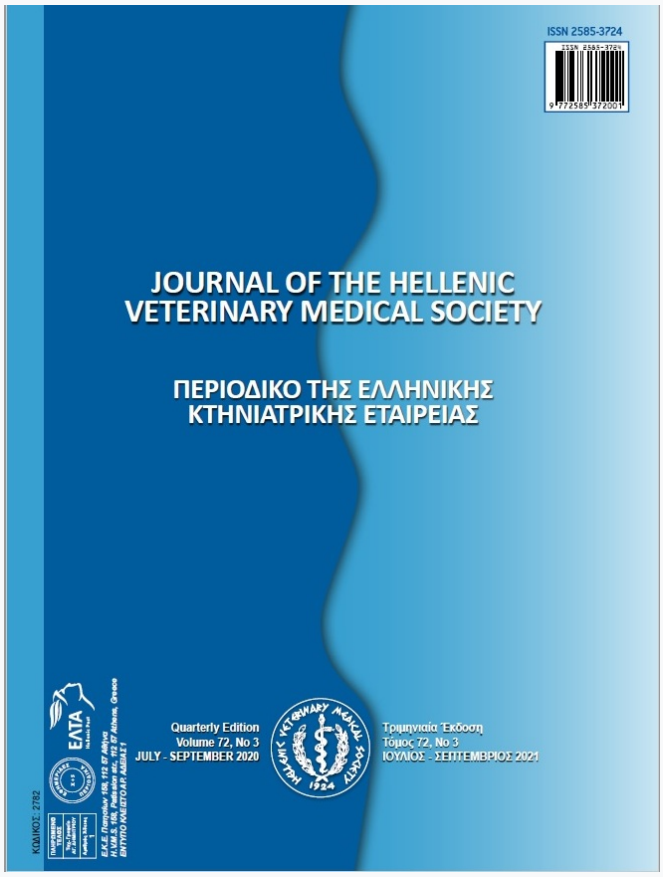

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Review article
Ανασκόπηση

Neuroacting drugs and its pharmacological response in relation to different stress status: A review

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ABSTRACT: This article intended to review many methods and types of stressors in the previous works of literature that describe the role of these stressors to induce modifications and alterations in the pharmacological response of the drugs acting on the nervous system (neuroacting drugs) in human and animal models. The current review focus on the different methods for inducing stress status which categorized as chemical, physical and miscellaneous stressors that affect on the well-known pharmacological response of the neuroacting drugs and by which mechanism can the stressor induce a modification in the drug target response with mentioning the findings related to changes in the pharmcologiacal response of the neuroacting drugs in previous literature. In conclusion, most studies suggest an alteration of the pharmacological response of neuroacting drugs, commonly by potentiating their efficacy and subsequent toxicity, due to different stressful methods, which may be obligated to the direct and indirect receptor modification (pharmacodynamic interaction) in addition to the direct pharmacokinetic influence on the essential parameters of absorption, distribution, metabolism, and excretion of the neuroacting drugs.

Keywords: animal model, interaction, neuroacting drugs, pharmacological response, stress

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INTRODUCTION

Stress means an increase in the free radical formation inside an organism's cells due to exposure to different stressful methods like chemicals, physical and other miscellaneous stressful agents (Lee and Jeong, 2007; Srivastava and Kumar, 2015). Different types of stressful methods causing an alteration in pharmacological response, especially for drugs that act on the nervous system. Stress may occur physiologically at the age of progressing and leads to an imbalance in the functions of the enzymes in the mitochondria responsible for energy production due to the accumulative effects of free radicals causing neurodegeneration (Navarro et al., 2002; Liguori et al., 2018). The goal of this review article was to focus on many methods and types of stressors in the previous works of literature that describe the role of these stressors with their mechanism for inducing modifications and alterations in the pharmacological response of the drugs acting on the nervous system in human and animal models because of the importance of the pharmacological response in the determining the actual benefits of using the drugs especially in clinical pharmacology.

BIOMARKERS USED FOR STRESS DETECTION

The state of oxidative stress (OS) is inferred using biochemical tests, the most important of which is the measurement of the glutathione and malondialdehyde concentrations, as well as the measurement of the total antioxidant status (TAS) (Dalle-Donne et al., 2006; Marrocco et al., 2017), which are among the essential vital signs indicating the occurrence of OS:

Glutathione: which consists of three peptide chains linked to the sulfur group; widely distributed in the organism's body and have an important and crucial part to metabolic as well as the defensive cell function by removing the free radical's toxicity that formed because of metabolic processes within the cell (Pastore et al., 2003; Dalle-Donne et al., 2006). Since the state of OS leads to a disruption of the antioxidant cellular biological defenses such as glutathione within the cells of the body of the organism, the state of the OS is inferred by measuring the glutathione concentration in the biological samples (e.g. Plasma and tissue) of the organism as its concentration decreases in the case of OS (Abdel Rahman, 1995; Patockova et al., 2003; Pastore et al., 2003; Dalle-Donne et al., 2006).

Malondialdehyde: The OS state occurrence leads to the cell membrane destruction of the body that contains unsaturated fats and this increases the level of the concentration of malondialdehyde compound, which is the final result of the lipid peroxidation process in the fat of the body cell membranes (peroxidation of unsaturated fatty acids, especially arachidonic acid). For this reason, the state of the OS is detected by measuring the malondialdehyde concentration (Patockova et al., 2003; Achuba et al., 2005; Del Rio et al., 2005; Dalle-Donne et al., 2006; Mendes et al., 2009), as the concentration of malondialdehyde rises, which is a sign of the stress. It is a toxic compound as it correlates with DNA and cellular proteins, causing genetic mutations, dysfunction of the cell, and a change in drug response (Marnett, 1999; Del Rio et al., 2005).

SELECTING AND CONSIDERING THE CENTRAL NERVOUS SYSTEM AS A TARGET FOR STRESS MODIFYING DRUGS

The central nervous system (CNS) differs from the rest of the body's systems by being more susceptible to stress (e.g., OS), due to its continued constant need for oxygen- significantly. It has a low concentration of antioxidants as well as has a high amount of polyunsaturated fats, and the fact that its large cellular compounds such as fats, carbohydrates, proteins, and nuclear acids that considered more susceptible to oxidation damage (Storz and Imlay, 1999; Patockova et al., 2003; Achuba et al., 2005; Sayre et al., 2008). The nervous tissue is more susceptible to the OS because of the production of high amount of free radicals. The reason is that the brain uses up to 20 % of the whole body oxygen, the CNS has a much amount of unsaturated fatty acids and the brain contains a high percentage of iron that stimulates metabolic processes. It has weak effectiveness of anti-oxidant enzymes, and these factors make the brain more susceptible to OS and thus have changed the effectiveness and pharmacological response to drugs that work on the nervous system (Pastore et al., 2003; Sayre et al., 2008).

TYPES OF STRESSORS

CHEMICAL STRESSORS

Hydrogen peroxide (H_2O_2): is one of the most common oxidizing compounds that stimulate free radical formation, the most important of which is the hydroxyl radical by Fenton Reaction. The hydroxyl radical is the leading cause of an OS that breaks down cell components, stimulates lipid peroxidation, and breaks down proteins, including protein receptors. It

stimulates regular or programmed death of the cell and is reliant on the concentration through direct oxidation of proteins and nucleic acids (Navarro et al., 2002; Patockova et al., 2003; Sayre et al., 2008). H_2O_2 reduces the effectiveness of dehydrogenases in the Krebs cycle, energy production, stimulates the growth factor and the receptor of the Aspartate neurotransmitter, which leads to an elevation in the calcium influx into the nerve cell and has a vital role for the serotonin receptor of rat brain, leading to poor behavior (Patockova et al., 2003; Sayre et al., 2008). Experimentally, H_2O_2 causes OS in chickens when given at 0.5% in water along with fourteen days and causes a neurobehavioral change in the open field activity (Mousa, 2012; 2014, Mousa and Mohammad, 2012a;b, Mousa, 2021; Mousa et al., 2021), besides modifying the pharmacokinetics (Mousa and Mohammad, 2012c).

Tertbutyl-hydroxyl peroxide: works by damaging the nerve cells in the brain by lowering body temperature and binding to the central and peripheral binding sites of the $GABA_A$ receptor on the outer surface of the mitochondrial membrane inside the neuron (Sarnowska et al., 2009).

Ethanol and nicotine: They cause OS by producing free radicals and depleting glutathione in the liver, kidney, lungs, and testes of rats, which is essential in the process of free radical disposal (Navasumrit et al., 2000; Husain et al., 2001).

Neuropeptide S: It induced OS, was found to alter the behavior of mice by causing a powerful OS that increases motor activity (Castro et al., 2009).

PHYSICAL STRESSORS

Mechanical immobilization: It has been observed that immobilization-induced stress by increasing the neurotransmitter dopamine level in the brain, and diazepam reduces the effects of this stress in rats (Hegarty and Vogel, 1995; Uehara et al., 2003). Restricting the movement of rats leads to stress. It alters activity measures used in the open field, as well as a change in behavior and a reduction of the glutathione of the nervous system (Nade and Yadav, 2010) while repeating restricting the movement, can induce stress in the rats and increases the neuron's sensitivity in the brain to diazepam which leads to an increased in its pharmacological response (Kalman et al., 1997).

Immersion: It was found that stress triggered by immersion by immersing chicken chicks in the water increased the number of places where the central benzodiazepine drugs were bound to the $GABA_A$ receptor, making these drugs closely bound to this receptor (Garcia et al., 2002).

Swimming: Which causes stress of rats (Motohashi et al., 1993) besides chickens (Marin and Arce, 1996) and increases the number of the benzodiazepine binding sites (central and peripheral) on the $GABA_A$ receptor of the nervous tissue without increasing number related to $GABA_A$ receptors, indicating an increased brain sensitivity to diazepam leading to an increase in its effect and pharmacological response to stress (Miller et al., 1987; Motohashi et al., 1993; Marin and Arce, 1996; Kalman et al., 1997).

Defeat Stress: It also increases the number of binding sites on the $GABA_A$ receptor in the brain without elevating the brain's number of $GABA_A$ receptors (Miller et al., 1987; Jie et al., 2018).

MISCELLANEOUS STRESSORS

Apomorphine: A drug that works on the CNS and is used as emetics causes OS in the rat brain and interferes with drugs that work on the nervous system and altering their pharmacological response (Moreira et al., 2003).

Xylazine: It was found that its administration with zolazepam and tiletamine in deer resulted in an OS in increasing the malondialdehyde concentration in the serum with rising glucose level (Yaralioglu-Gurgoze et al., 2005).

Chlorpyrifos: This is an insecticide that was found to cause OS in rats with an elevation in the process of lipid peroxidation of the red blood cells, indicating that it could interfere with the drugs administered with it (Mansour and Mossa, 2009).

Minerals (Cadmium, lead, mercury, and arsenic): They were found that exposure to these minerals causes OS by depleting antioxidants levels, which leads to increased active oxygen with rising of radicals such as the hydroxyl root besides high oxide root leading to the breakdown of proteins, fats, DNA, and the toxicity mechanism of these minerals may be attributed to their ability to cause OS (Storz and Imlay, 1999; Ercal et al., 2001; Jemai et al., 2007).

Sodium fluoride: causes OS, as this was inferred by the increase in the malondialdehyde concentration in the plasma of mice (Altintas et al., 2010).

MECHANISM OF STRESS INDUCTION

Only, the stressful agents are causing an elevation in the hydroxyl group (OH^-) (Fenton reaction), causing free radicals to be formed called Reactive Oxygen Species (ROS), which interact and destruct the cellular components like proteins (e.g., Receptors), carbohydrates, lipids, and nuclear acids (Figure 1) (Kar and Choudhury, 2016).

STRESS INDUCES A MODIFICATION IN THE BLOOD-BRAIN BARRIER

Many stressful methods destroy the blood-brain barrier (BBB), which may lead to more passage of the drugs acting on the nervous system. OS plays a role in increasing the permeability of the substance of the blood (e.g., Drugs) to the CNS through the BBB, which has an essential function in the balance of the CNS, as it was found that the OS works to change the location of the occludin (a protein responsible for the vital link between tight junction between the barrier cells) which increases the barrier's influence over substances and drug infiltration between the blood and the CNS (Lochhead et al., 2010; Daneman and Prat, 2015).

STRESS VERSUS NEUROTRANSMITTERS OF THE NERVOUS SYSTEM

Stressful agents that formed free radicals interact with the synthesis and release of the neurotransmitters in the presynaptic neuron in addition to its modification of the neurotransmitters' affinity and efficacy on their receptors on the postsynaptic neurons (Figure 2) (Kar and Choudhury, 2016). OS plays a significant part in the pathogenicity of multiple sclerosis, that destroys the myelin and axonal parts of neuron as well as free radical elevation, a decrease in concentrations of antioxidants in the blood and cerebrospinal fluid, and an increase in the neurotransmitter glutamate during the disease occurrence (Sayre et al., 2008). OS is causing degenerative diseases of neurons, affecting their susceptibility to neurotransmitters' secretion (Sayre et al., 2008). The OS destroys the neurons that produce Catecholamines such as adrenaline, noradrenaline, and dopamine in the brain, thereby leading to neurological diseases, including Parkinson's disease (Sayre et al., 2008). The H_2O_2 that causes OS destroys nerve cells in the brain of rats that producing neurotransmitters such as dopamine (Hussain et al., 1995) and it causes oxidation in the neurotransmitter dopamine to neurotoxic compound (Sayre et al., 2008). It was found that H_2O_2 increases the secretion of dopamine and noradrenaline neurotransmitters from the neurons of the brain of rats and increases their effect on their receptors by inhibiting the reuptake of these neurotransmitters into the neuron (Langeveld et al., 1995). H_2O_2 is used to induce OS and study neuropathological effects in the brain because it stimulates glutamate receptors by increasing secretion, increasing Nitric Oxide production, increasing the percentage of programmed neuronal cell death (Apoptosis) (Fatokun et al., 2007). The OS is the causative agent of diseases, neuropathy, and the cause of epilepsy cases, as it was found that stimulating the receptor of glutamate leads to the occurrence of these cases (Coyle and Puttfarcken, 1993).

EFFECT OF DIFFERENT STRESS METHODS ON THE PHARMACOLOGICAL RESPONSE OF SOME DRUGS ACTING ON THE NERVOUS SYSTEM

It was found that OS destroys the cell membrane by the lipid peroxidation process and leads to a change in the cell membrane's biological properties, including fluid entering the cell and disrupting or losing the receptor function in the cell membrane (Dalle-Donne et al., 2006; Donne et al., 2006). Stress factors involved in modulating the pharmacological responses of some neuroacting drugs were illustrated in Table 1.

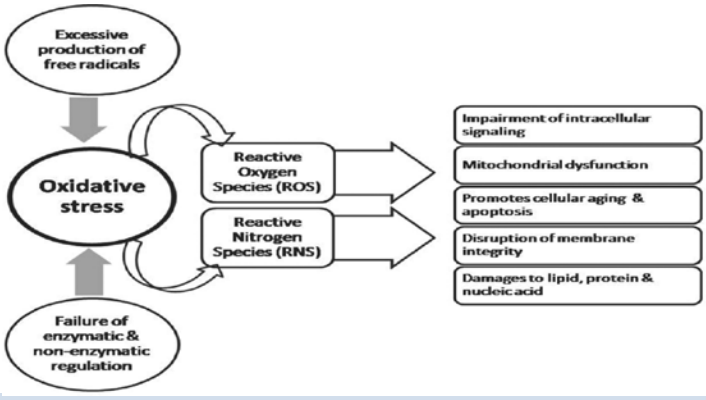

Figure 1. Flow chart of the impact of the OS on the cellular components (Kar and Choudhury, 2016).

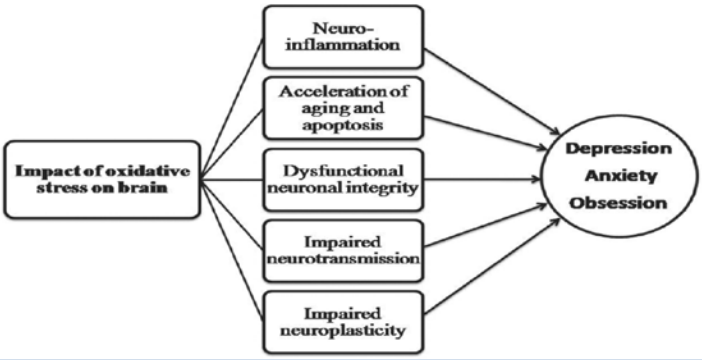

Figure 2. Flow chart of the OS involved in neurotransmitters and neuronal dysfunction (Kar and Choudhury, 2016).

Table 1. Summary of the stress factors involved in the modulation of the pharmacological responses of some neuroacting drugs

Stress factor	Neuroacting drug	Model	Drug response	Theory of interaction	Reference
H_2O_2	Diazepam	Chickens	+	+ affinity; -metabolism and excretion; K channels opening; modify pharmacokinetic parameters	Mousa and Mohammad, 2012a; 2012c; Zhang et al., 2002
	Xylazine	Chickens	+	+ affinity; - metabolism and excretion	Mousa and Mohammad, 2012b
	Ketamine	Chickens	+	+ affinity; - metabolism and excretion	Mousa, 2014
	Propofol	Chickens	+	+ affinity; - metabolism	Ahmed, 2010
	Detomidine-ketamine	Rabbits	+	Down regulation; - metabolism	Wohaieb et al., 1994
	Pentobarbital	Rats	+	+ affinity; - metabolism	Mohammad et al., 1999
	Neuroleptics	Rats	-	Activating Ca^{+2} channels; - NT release	Akaishi et al., 2004
	Benzoquinone	Rats	-	- affinity and metabolism	Baigi et al., 2008
	Chlorpyrifos	Rats	+	+ free radical formation	Mehta et al., 2009
	Paraquat	Rats	+	+ lipid peroxidation	Weidauer et al., 2004
	Antiepileptic drugs	Humans	-	+ lipid peroxidation; - antioxidant defense mechanism	Lopez et al., 2007
Cadmium	Detomidine-ketamine	Mice	+	+ oxidative damage in the CNS	Mohammad, 1994
	xylazine	Mice	+	+ inhibition of the CNS	Mohammad et al., 2000
Doxorubicin	Diazepam	Humans	+	+ inhibition of the CNS	Abdel Baky and Ali, 2009
Ethanol	Neuroacting steroids	Rats and Humans	+	+ basal levels	Porcu and Morrow, 2014
Nicotine	Propofol	Rats	+	Changes in brain metabolism	Khokhar and Tyndale, 2011
Immersion	Benzodiazepines	Chickens	+	+ affinity	Garcia et al., 2002
Restraint	Endotoxin	Mice	-	+ Glucocorticoid release	Kasahara et al., 2015
Foot shock	Neuroacting steroids	Rats	+	+ $GABA_A$ receptor function	Barbaccia et al., 1996

+: Increase; -: Decrease; NT: Neurotransmitter; CNS: Central nervous system

STRESS-INDUCING PHARMACODYNAMIC INTERACTION

Stress can induce a modification in the pharmacological response of the neuroacting drugs in one or more ways through increasing the binding sites at the receptors, increasing the receptors' susceptibility, and decreasing the numbers of the receptors (down-regulation). The stress can reduce the RNA production, which inhibits the development and production of protein substances in the cell, including protein receptors within the cell and those on the cell membrane, causing a reduction in the receptors' number (Crawford et al., 1997; Gunn et al., 2015).

STRESS-INDUCING PHARMACOKINETIC INTERACTION

Stress modifies drug disposition and availability to the target receptors by increasing the absorption of the drug from the site of treatment and alters their distribution by the destruction of the protein binding while decreasing the metabolism by affecting the cytochrome P_{450} enzymes responsible for drug elimination and effect termination and later decrease drug excretion (Mohammad et al., 1999; Mousa, 2012; Mousa and Mohammad, 2012c).

CONCLUSIONS

In conclusion, there are many methods of stressors used for induction of stress in animal models like chemical, physical and miscellaneous stressors and the majority of them practices the chemical method by using H_2O_2. Most studies suggest an alteration of the pharmacological response of neuroacting drugs, commonly by potentiating their efficacy and subsequent toxicity, due to different stress methods, which may be obligated to the direct and indirect receptor modification (pharmacodynamic interaction) in addition to the direct pharmacokinetic influence on the essential parameters of absorption, distribution, metabolism, and excretion of the neuroacting drugs**.**

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CONFLICT OF INTEREST

None declared.

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