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Haloperidol Cytotoxicity and Its Relation to Oxidative Stress

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Abstract: Haloperidol (HP) is used for the symptomatic treatment of psychosis, manic phases, hyperactivity, aggressiveness, and acute delirium. Long-term use leads to various adverse side effects, especially to severe impairment of extrapyramidal nerve tracts and in particular, altered QT interval and increased incidence of arrhytmias. It is believed that cytotoxicity of HP and its metabolites is responsible for both neurotoxicity and cardiotoxicity. Extrapyramidal and cardiac adverse side effects may be explained by the HP-induced oxidative stress, as implicated by many studies. HP was reported to induce lipid peroxidation with subsequent membrane changes, responsible for cell death. Vice versa, cells resistant to oxidative stress are also resistant to the toxic effects of HP. Similarly, high percentage of patients suffering from extrapyramidal symptoms treated by vitamin E and other lipid-soluble antioxidants demonstrates diminishing of these adverse side effects. HP's ability to induce oxidative stress by multi-modal action (increased metabolism of dopamine, decrease of glutathione content, induction of NF-κB transcription factor, and inhibition of complex I of respiratory chain) has been established just recently. This review brings summarizing view on the cytotoxicity of haloperidol and involvement of reactive oxygen species and oxidative stress HP-induced cytotoxicity.

Keywords: Arrhytmia, cardiotoxicity, dopamine, haloperidol, oxidative stress, Torsade de Pointes.

HALOPERIDOL, ITS METABOLISM, METABOLITES AND SIDE EFFECTS

Haloperidol (HP) belongs to the group of typical incisive antipsychotics [1]. It is highly potent drug used particularly in the management of acute states, such as psychosis, manic phases, hyperactivity, aggressiveness, and acute delirium; in some cases, it is administered on a long-term basis [1, 2]. HP was first synthesized in 1956 and four years later it was introduced into clinical practice. Due to its relatively good tolerance and low price it became one of the most widely used antipsychotic drugs. Chemically, it belongs to butyrophenones. It is metabolised via N-dealkylation by cytochrome P450 in liver [3], with the preferential involvement of CYP 3A4 isoenzyme [4, 5]. Average haloperidol elimination half-time after intravenous administration in the dose of 0.125 mg/kg is approximately 17.9 ± 6.4 hours [6].

The main mechanism of action of HP and other typical antipsychotics is the blockage of dopamine D2 receptors (DRD2), particularly in mesolimbic and mesocortical system. HP acts as a high affinity D2 antagonist. In addition, high affinity of HP was proven also to sigma receptors, both σ1 and σ2 [7, 8]. Affinity to these receptors is of such magnitude that even just one orally administered dose (causing plasmatic nanomolar concentration of HP) is sufficient to cause sigma receptors occupancy [9].

Like in the most of typical antipsychotics, severe adverse side effects were reported after HP treatment. Among those, impairment of extrapyramidal nerve tracts with subsequent patient mobility disorders or tardive dyskinesia are mostly pronounced [10]. Namely, HP in addition to its therapeutic antidopaminergic effect affects also other structures in diverse localizations, particularly nigrostriatal system. Shivkumar *et al.* observed that increasing HP dosage led to the increased damage of extrapyramidal nerve tracts in rat model [10]. Furthermore, supersensitivity of dopamine receptor and tardive dyskinesia persistence after interruption of the HP therapy were observed [11].

In addition to extrapyramidal manifestation, cardiotoxicity of HP represents the most serious adverse effect. It has been repeatedly reported that HP prolongs the QT interval and thus increases the risk of the arrhythmias of the Torsade de Pointes (TdP) type that may result in sudden cardiac death. QT prolongation and subsequent arrhythmias occurred after administration of HP both orally and intravenously [12, 13],

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and as a result of HP overdose [14]. Moreover, Blom *et al.* found that impact of HP on QT depends on patient's history. Whereas QT prolongation was observed in patients with normal QT before HP treatment, QT shortening was observed in patients with prolonged QT before HP administration [15]. Undergoing an extensive surgery prior to HP treatment has been proved as an additional risk factor for QT prolongation [15].

It is worth mentioning that TdP represent relatively common result of hypokalemia and hypomagnesaemia. Evidence, that this mechanism is responsible for HP-induced TdP is supported by studies by Satoh *et al.* and Jabotinskyrubin *et al.* These authors found that HP treatment results in the reduction of the magnesium plasma levels [16] and magnesium administration acts antiarrhytmically in haloperidol-overdosed animals [17]. Higher heart rates caused by haloperidol-induced voltage independent block of the transient outward K^+ current in cardiomyocytes may be the next possible factor in HP-induced cardiotoxicity [18, 19, 20].

HP effects were studied also at cellular level. It was concluded that HP triggers necrosis rather than apoptosis [21]. However, in tumour tissue, haloperidol binding to the sigma receptors is followed by the triggering the apoptotic processes [22].

HP VARIABILITY BY ETHNICITY

Drugs and other xenobiotics are metabolised by enzymes, activity of which varies among individuals, ethnic groups, and races [23, 24]. Asians had significantly higher concentration of HP in the blood serum as compared to white Americans after administration of the same dose [25, 26]. As a result, interracial differences were observed in HP doses that are capable to induce side effects [27, 28]. Binder and Levy observed that impairment of extrapyramidal nerve tracts two weeks after initiation of treatment with HP occurred in 95 % of Asians, 67 % Caucasians, but only in 60 % of African-Americans [29]. Jann *et al.* confirmed that the Chinese are predisposed to extrapyramidal nerve tracts impairment during the HP therapy. In summary, results of these studies indicate that Asian population shows the highest differences in responses to HP as compared to other ethnics. As a result, schizophrenics of Asian origin may benefit from the therapy by lower HP doses [30].

FREE OXYGEN RADICALS AND OXIDATIVE STRESS

Free oxygen radicals are highly reactive entities with unpaired electron in the outer orbital. Oxygen species (ROS – Reactive Oxygen Species) include superoxide anion radicals, hydroxyl radicals, hydrogenperoxides, singlet oxygen and others, and are produced mainly as a result of an aerobic respiration [31]. ROS are generated also in the β-oxidation of fatty acids, metabolism of xenobiotics via cytochrome P450, in the redox cycling of quinones, stimulation of phagocytes and metabolism of dopamine. ROS can damage proteins, lipids, cell membranes and membrane structures and nucleic acids, including DNA [32].

Under the physiological conditions, organism is protected against negative and harmful effects of free radicals by complex system of antioxidant enzymes. The most important antioxidant enzymes are superoxid dismutase (SOD), catalase (CAT), and glutathion peroxidase (GSHPx). The basic mechanisms of this antioxidant system are overviewed in (Fig **1**). The balance between ROS and antioxidant cell protection is essential for the correct cell functions. Disturbance in this balance toward the ROS superiority leads to the oxidative stress and subsequently to necrotic or apoptotic cell death [33, 34].

Oxidative stress may be manifested in a body in many ways. The most important symptoms of the oxidative stress are lipid peroxidation and increased production of antioxidant enzymes, induction of transcription factors and activation of MAP kinases.

Lipid Peroxidation and Increased Production of Antioxidant Enzymes

Increased production of SOD and CAT occurs immediately after exposition of organism to ROS and oxidative stress [35], however, production of these enzymes gradually decrease under the chronic exposition of organism to ROS, because enhanced biosynthesis of these enzymes is very burdensome for organism [36].

Induction of Transcription Factors, such as NF-κB

NF-κB (nuclear factor kappa B) is a ubiquitous rapid response transcription factor in cells involved in immune and inflammatory reactions. It binds to regulation sequences of numerous genes [37]. NF-κB is activated in the cells by many ways, especially by oxidative stress and increased amount of hydrogen peroxides [34]. NF-κB is also activated by the signals of necrotic cells [38]. Enhanced NF-κB activity may be blocked by antioxidants [39].

Activation of MAP Kinases

Mitogen-activated protein kinases (MAPKs) are serine/threonine kinases that are crucial in signal transduction in many signal pathways in cells. They are usually stimulated by growth and differentiation factors.

MECHANISM OF HP-INDUCED CYTOTOXICITY

Behl *et al.* established that the cells resistant to oxidative stress are also resistant to the toxic effect of HP [21] which implicates the role of free radicals in the HP-induced cytotoxicity. ROS are generated in the process of oxidative deamination at the degradation of dopamine by monoamine oxidase B (MAO-B) [10]. Chronic treatment by HP induces fluctuations in dopamine level and thus increases oxidative stress of organism [10]. These reactive metabolites of dopamine – especially hydrogen peroxide – may in the presence of catalysts, such as ferrous ions, contribute to the generation of highly neurotoxic hydroxyl radicals that are involved in the lipid peroxidation [40]. Free haemoglobin and myoglobin may – due to the presence of iron ions in their structure – enhance the damage of cells suffering from oxidative stress, i.e. the cells with increased hydrogen peroxide level. Free haemoglobin and myoglobin can occur at a brain haemorrhage [40]. Indeed, patients suffering from

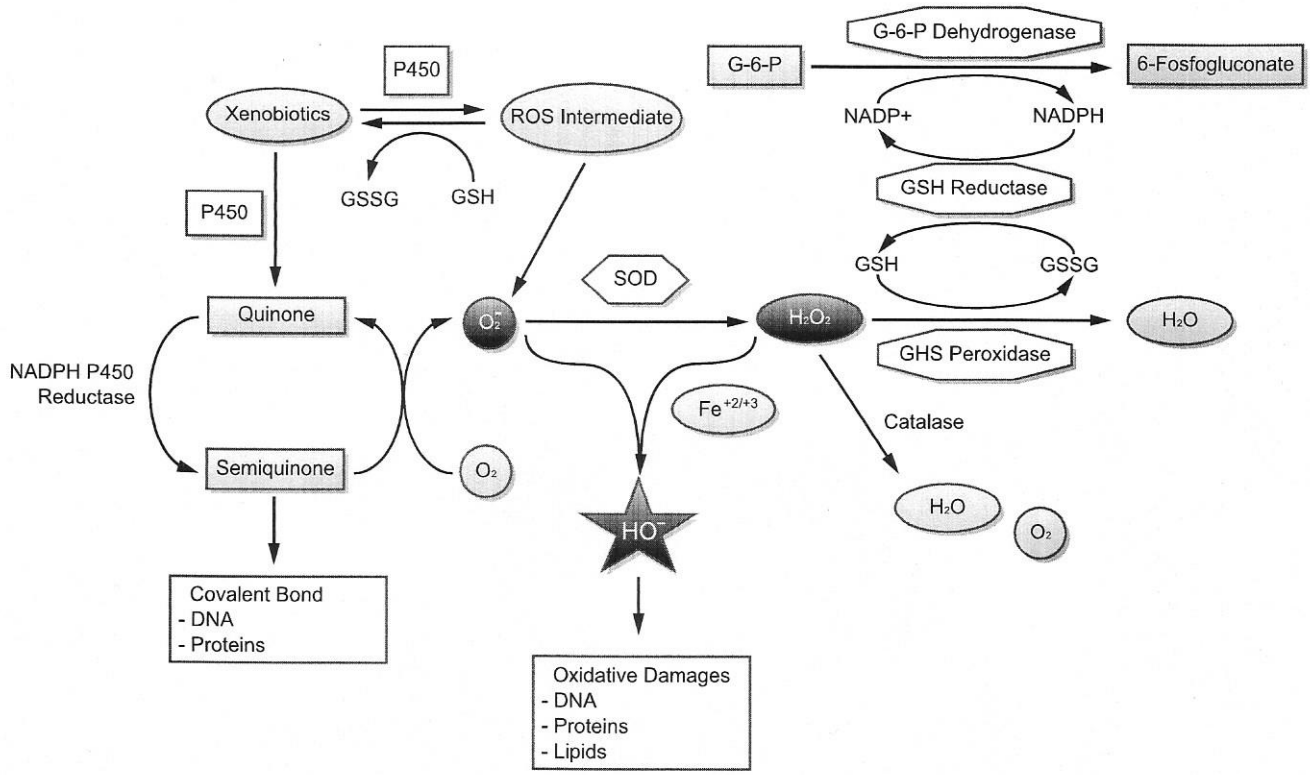

Fig. (1). Basic mechanisms of the generation of free radicals and involvement of antioxidant systems in the protection of cells against ROS. Superoxid dismutase (SOD) catalyzes the dismutation of superoxide into oxygen and hydrogen peroxide; it is involved in the detoxication of superoxide anion radicals – $O_2^{\cdot-}$. Catalase (CAT) and glutathion peroxidase (GSHPx) catalyze decomposition of hydrogen peroxide (H_2O_2) and its conversion to water. In the presence of transition metals (Fe^{2+}, Cu^{+}) H_2O_2 is reduced in Fenton´s reaction and highly reactive and toxic hydroxyl radical occurs. Semiquinone is a highly unstable free radical that is together with $O_2^{\cdot-}$ generated in the redox cycling of quinones in the respiration chain. It is able to covalently bind DNA and proteins and form DNA adducts.

brain injury simultaneously treated with HP have repeatedly shown an increased risk of neuroleptic malignant syndrome as a result of adverse effects of HP [41, 42]. Lipid peroxidation caused by ROS is responsible for the changes in synaptic signals (lower transport of γ-aminobutyric acid and dopamine into pre-synaptic vesicles) [43]. Direct connection between the hydrogen peroxide production and HP was established by Post *et al.* when accumulation of hydrogen peroxide was observed in immortalized cells of mouse hippocampus after addition of HP into cultivation medium. Addition of HP affected also amount of intracellular glutathione (GSH): whereas during the first hours after the HP administration the GSH level increased, after 16 to 20 hours a dramatic decrease in GSH level was observed (which means increase of oxidative stress) in the treated cells as compared to controls [39]. In addition, high percentage of patients suffering from extrapyramidal symptoms treated by vitamin E and other lipid-soluble antioxidants demonstrates significant diminishing of these adverse side effects. This fact is in agreement with the theory that the adverse side effects of HP are caused by increased lipid peroxidation and subsequent cell death in neuronal cells [44].

Hodnick *et al.* ascertained that neuroleptics such as HP inhibit enzyme NADH:ubiquinone oxidoreductase, complex I of the respiratory chain. Despite the fact that respiratory chain is the main source of the ROS in organism, its inhibition, although a ROS decrease would be expected, more likely leads to the ROS generation [31]. Inhibition of the complex I of the respiratory chain may be one of causes of irreversible damage of extrapyramidal nerve tract in patients treated by neuroleptics [45].

HP AND GENE EXPRESSION

DRD2

HP is a dopamine antagonist, so its main target is a dopamine receptor. Dopamine receptors are classified into two groups: D1 and D5 belong to the group of D1-like receptors, D2–D4 belong to the group of D2-like receptors. These two groups differ basically in their effect on postsynaptic neuron. Activation of D1-like receptors may lead to the excitation and inhibition of postsynaptic neurons, whereas activation of D2-like receptors leads more likely to inhibition. HP binds to D2 receptor (DRD2). It has been established that HP affects not only signalization of DRD2 receptor, but also the expression of *DRD2* gene. Long-term administration of HP increased *DRD2* mRNA production on one hand and down-regulated expression of D1 and D5 subtypes on the other hand, although these subtypes have only minimal affinity to HP [46].

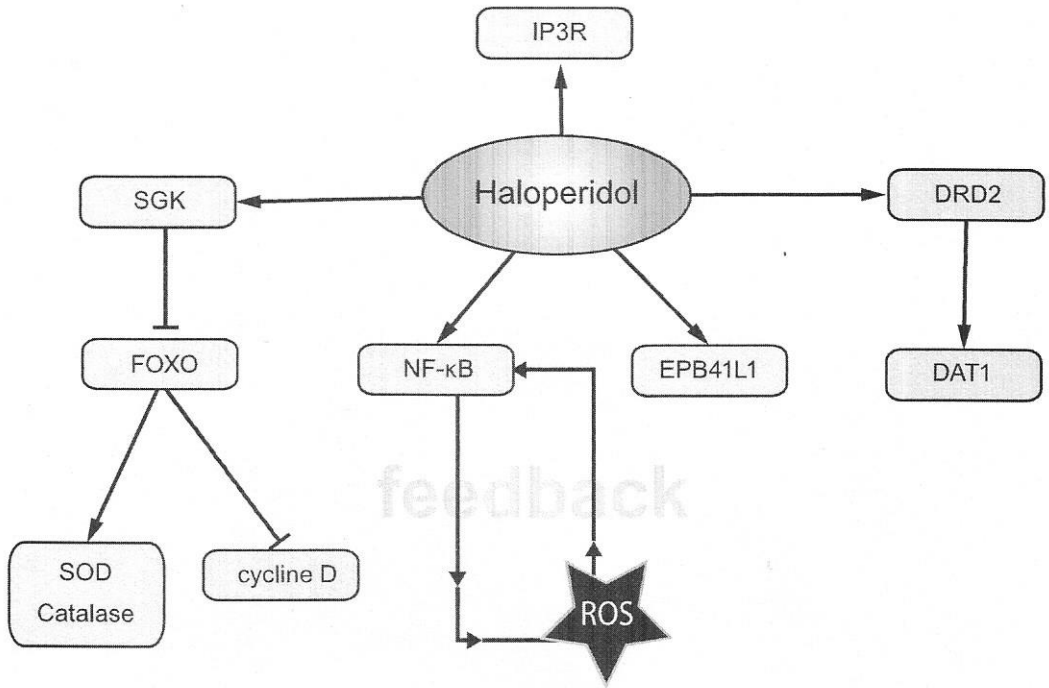

Fig. (2). Effect of HP on the gene expression. DRD2-dopamine receptor D2, DAT1-dopamine transporter 1, IP3R-inositol trisphosphate receptor, SGK-serum- and glucocorticoid-induced protein kinase (SGK protects synaptic glutamate transporters against degradation in proteasomes), FOXO-transcription factor from the family of FOX factors, SOD-superoxid dismutase, EPB41L1-erythrocyte membrane protein band 4.1-like protein 1 (multifunctional protein that mediate the interaction between D2 and D3 dopamine receptors and plasma membrane of neurons), NF-κB-nuclear factor kappa B (participates in the positive regulation of inflammatory responses), ROS-reactive oxygen species. ⊥ inhibition, ↓ activation

DAT1

Dopamine transporter (DAT1) is an integral membrane protein, the most important regulator of the active dopamine re-uptake from the synaptic cleft; its expression is activated by HP treatment [47].

Sigma-1 R a IP3R

Long-term administration of HP leads to up-regulation of σ1 receptors in both rat heart atria and ventricles. Receptors for inositol 1,4,5-trisphosphate are increasingly expressed only in the neuronal cells of atria. These changes in both receptor families affect availability of Ca^{2+} in the cytoplasm of myocardial cells and thus modify the myocardium contractility [48]. Concurrently, the changes in σ1 and IP3 receptors expression may help to elucidate the QT prolongation and origin of severe arrhythmias of the Torsade de Pointes type during the HP therapy.

SGK

Glucocorticoid-induced protein kinase (SGK) protects synaptic glutamate transporters against degradation in proteasomes [49]. In addition, it inhibits expression of the FOXO transcription factor that is involved in the positive regulation of antioxidant enzymes SOD and CAT expression and in the negative regulation of cyclin D expression [50]. Treatment by HP leads to up-regulation of SGK [49].

EPB41L1

EPB41L1 (Erythrocyte membrane protein band 4,1-like protein 1) is a protein stabilizing DRD2 and DRD3 on the plasma membrane of neuron. Its expression is enhanced after HP treatment [47].

Effect of HP on the expression of above-mentioned genes is summarized in (Fig. **2**).

CONCLUSION

Haloperidol (HP) has been introduced into clinical practice in the 1960s and soon has begun commonly used in the treatment of many psychiatric disorders, especially acute and chronic schizophrenia. Blocking of dopamine receptor (DRD2) was the only well-know mechanism of its effect for many years. Later, the adverse side effects, especially extrapyramidal symptoms, were studied. HP's ability to induce oxidative stress by multi-modal action (increased metabolism of dopamine, decrease of glutathione amount, induction of NF-κB transcription factor, inhibition of complex I of respiratory chain) has been proposed only recently. The final effect of increased oxidative stress consists in the lipid peroxidation and damage of biomembranes resulting in synaptic signals changes. Other mechanism of the adverse side effects of HP is based on the activation and general regulation (up- or down-regulation) of gene expression. Products of these changed gene expressions are involved in the regulation of many cellular processes, such as signal

transduction in cardiomyocytes, antioxidant barrier against oxidative stress, cell division and proliferation, inflammation, etc.

Haloperidol represents an example supporting the idea of necessity to study and know the exact mechanisms of drug effects, possible differences in the dosage within various ethnic groups, and general impact of drug in the context of the whole organism.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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ABBREVIATIONS

CAT	=	Catalase
DAT1	=	Dopamine transporter
DRD2	=	Dopamine D2 receptor
EPB41L1	=	Erythrocyte membrane protein band 4,1-like protein 1
GSH	=	Glutathione
GSHPx	=	Glutathion peroxidase
HP	=	Haloperidol
MAPK	=	Mitogen-activated protein kinase
MAO	=	Monoamine oxidase
NF-κB	=	Nuclear factor kappa B
ROS	=	Reactive Oxygen Species
SGK	=	Glucocorticoid-induced protein kinase
SOD	=	Superoxid dismutase
TdP	=	Torsade de Pointes

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