ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Review Article

GENOTOXICITY AND ITS MECHANISM OF ANTIDEPRESSANT AND ANTIPSYCHOTIC DRUGS: A REVIEW

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ABSTRACT

Antidepressants and antipsychotics are the CNS drugs which are used to treat CNS disorders like depression and psychosis respectively. They are known to act upon their respective receptors in the brain and stabilize the condition. Knowing to have a few side effects and extrapyramidal effects for the drugs, genotoxicity was also one of the major adverse effects of such drugs. Identification of genotoxic antidepressants as a long term medication is important to avoid their prescription. This review gives knowledge about the mechanism of action of the drugs through which they cause the toxic effect on the genetic material. It is known the reactive oxygen species play a major role in causing the maximum damage to the DNA. Few antidepressants like Fluoxetine, sertraline and antipsychotics like chlorpromazine, Phenothiazine are known to cause the high degree of toxicity when compared to other such drugs of the same category. This review provides a piece of basic information regarding the genotoxic effects of antidepressants and antipsychotic drugs.

Keywords: Genotoxicity, Antidepressants, Antipsychotics, Reactive oxygen species, Toxicity

1. INTRODUCTION

There are various CNS disorders such as mania, Alzheimer's, psychosis, multiple sclerosis, depression, parkinsonism, etc. out of which depression and psychosis are significant disorders that have developed In recent times. Depression is a complex disease characterized by disturbances of the mind that may be expressed as irritability, insomnia, fatigue, agitation, psychomotor alterations, feelings of guilt and inadequacy, concentration disturbances, and a suicidal tendency. Various exogenous and endogenous factors form the origin of this [1]. Psychosis is a common and functionally disruptive symptom of many psychiatric, neurodevelopmental, neurologic, and medical conditions. Schizophrenia is the characterizing feature of Psychosis, a typical but variable feature of mood and substance use disorders, and a relatively common feature of many developmental, acquired, and degenerative neurologic and medical conditions. Over these conditions, psychosis is both a contributor to disability and a barrier to productivity and participation [2]. Such referenced conditions are dealt with utilizing antidepressants and antipsychotics respectively and patients are relatively watched for changes in their behaviour and mood. These drugs are used majorly given for long term use to numberless patients3. Antidepressants lead to the symptomatic decrease of the depressive condition. They were first developed in the 1950s and have been used regularly since then. More than 30 types of antidepressants are available currently which mainly includes Tricyclics, Monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs) [3]. Whereas antipsychotic drugs were developed since 1989 and there are various variety of newer antipsychotics presently. These drugs are known to for its substantial improvement in CNS disorders such as schizophrenia and related disorders [4]. Where the number of overdose cases has been found to increase in case of antipsychotics [5]. It was found that 57 antipsychotics and 47 antidepressants are on the market according to the 2007 edition of the Martindale-The Complete Drug Reference (2007) and in several countries, it has been used extensively. The International Agency for Research on Cancer (1972-2007) in the 91 volumes of IARC Monographs on the Evaluation of Carcinogenic Risks to Humans published in the years from 1972 to 2007 examined 203 drugs that are known to have a genotoxic effect. Which includes the family of antidepressants and antipsychotics, but it was considered

non-classifiable under carcinogenicity due to inadequate evidence in humans and a few pieces of evidence in case of animal study. According to a review of Snyder and Green [6] on the genotoxicity of marketed pharmaceuticals, and information based on 1999 edition of the Physicians' Desk Reference as well as from the peer-reviewed published literature, it was found that about 34 antipsychotics and antidepressants are genotoxic, but there was no exact evidence reported for 14 such drugs and the information regarding few such drugs were quite limited. This review is a compendium of genotoxicity and carcinogenicity study of few of antidepressants and antipsychotics that have been found in an extensive search. The above data was according to the search that was conducted primarily in peer-reviewed journals using Medline, Topline, and the Registry of Toxic Effects of Chemicals Substances (U.S. Department of Health and Human Services, 1987).

2. MECHANISM OF ACTION

2.1. Antidepressants

Recent studies have found that tricyclic antidepressants and its family have the capability to induce free radicals and oxidative stress *in vitro* [7]. These oxygen-derived species which include free radicals cause DNA damage that is of the most frequent type encountered by aerobic cells [8]. Xia et al. [9] investigated that clomipramine belonging to the TCAs class of antidepressants could trigger the apoptotic action in lymphocytes. Clomipramine has strong selectivity between normal and cancer cells and hence it posses non-toxic cancer therapeutic effect. It is known that the changes in the cell cycle and chromatin distribution in c6 glioma cells is mainly due to dBcamp and hence it leads to inhibition of the substantial cell population at the g1 phase. It is also accompanied by chromatin condensation where it only reflects on a certain part of chromatin. This may lead to halting of the cells from the usual cycling process or cause the changes in genome expression which is responsible for the simultaneous differentiation of cells [10]. Two ways of DNA damage is, directly and indirectly, *i.e.* radical-mediated nuclear damage and other is due to downstream consequences of receptor-mediated action at numerous other sites of the cellular damage respectively. The single-strand breaks that are induced by the oxidative stress due to antidepressants can be assessed by the DNA repair enzymes and alkaline single-cell electrophoresis. Antidepressants at the therapeutic dose are known to cause direct DNA interaction or indirectly after the metabolic transformation which leads to genotoxic damage and establish their genotoxicity and its intensity [1]. Ishii et al. [11] found that when caffeine and mitomycin C added to the human lymphocytes during G2- and S- phase of cell cycle they produced sister chromatid exchange(SCE) and chromatid aberrations. From which they concluded that the formation of SCE occurs during the S-phase and chromatid aberrations in the G2-phase, may also be seen in case of antidepressants in a much similar manner as that of caffeine and mitomycin C [12].

2.2. Antipsychotics

Perturbation of the cell machinery is one of the major aspects where it may lead to DNA demethylation and genotoxic damage at the level of the replication fork, producing an increase of the error-prone ligation. It was found that there is an increase in the genotoxicity causing DNA damage in mammalian cells which may be due to the demethylating chemicals [3]. The accumulation of active metabolites of CLZ was found to exhibit genotoxicity, agranulocytosis and hepatoxicity [13]. And, the in vitro studies demonstrated that four different primary oxidative metabolites (NDM olanzapine, 7-OH olanzapine, 2-OH olanzapine and N-O olanzapine) were formed from OLZ by human microsomes [14]. The cytotoxicity that was observed on association with these drugs is due to the oxidative stress and production of ROS (reactive oxygen species) which was reported that it gets incorporated and implicate the clinical adverse effects of antipsychotics We may suggest that cytotoxicity of these drugs is associated with oxidative stress since oxidative stress and the concomitant production of reactive oxygen species (ROS) have been incorporated and implicated in the clinical adverse-effects of [15]. And, Dietrich-Muszalska et al in 2009 proved that when treated with antipsychotics for schizophrenic patients there may be oxidative or nitrative modifications of plasma proteins which may be due to production of ROS and reactive nitrogen species [16]. It was reported that psychogenic stress can lead to an increase in the sister chromatid exchange (SCEs). Fischman et al. [17] have studied the activity of antipsychotics that was found to induce acute psychogenic stress in rats that led to genetic damage both at the chromosomal and molecular levels. Few authors have also conducted long term studies to known the effect of a prolonged period of stress, the endocrine action on the effect and also to find the relation between psychogenic stress and chemical

mutagens [18]. It was found that there was an elevation of SCEs and chromosomal aberrations levels that prove it induces genotoxixity [17]. Chlorpromazine which possesses non-discriminatory inhibitory effect against DNA-repair-proficient and repair-defective strains were evaluated for the studies. It is plausible to suggest that mutations could have been induced in the susceptible tester strains during the repair processes of the DNA-induced lesions by chlorpromazine [19]. The susceptibility of strain TA102 to chlorpromazine in mediating frame-shift mutations and the non-susceptibility of TA97 indicated that chlorpromazine has a preferential affinity for the A: T-rich sequences of nitrogenous bases of the DNA.

3. MAJOR DRUGS CAUSING TOXICITY

When evaluated it was found that on considering benefit/risk ratio these drugs might cause the occurrence of a genotoxic and carcinogenic effect as an adverse drug reaction which cannot be excluded. The recent study has been reported the drugs from these two families appeared to be positive when tested for genotoxicity and carcinogenicity in the case of humans. It was reported that 57 drugs from these two families showed at least one test positive when evaluated for genotoxicity and carcinogenicity, out of which 24 drugs are antipsychotics and 33 antidepressants drugs [3].

3.1. Antidepressants

Antidepressants are known to exert DNA damage in human leucocytes, but the rate of incidence differs from drug to drug. Research shows that fluoxetine, sertraline and clomipramine are the potent antidepressants drugs that induce DNA damage with fluoxetine produced the most, sertraline produced the intermediate and clomipramine produced the least damage. Fluoxetine a selective serotonin reuptake inhibitor class of drug causes the maximum DNA damage and clomipramine the least. The aerobic cells encounter the free radicals and the oxygen-derived species which leads to DNA destruction [2]. The authors have evaluated fluoxetine and found that it has pronounced DNA damage activity and they also reported that the DNA breaks occurring after 24hr of the fluoxetine treatment was due to the apoptotic activity [10]. These results were also found to be similar to that of imipramine and few other antidepressants. Imipramine is found to increase the reactive oxygen species that could lead to an increase in the apoptotic process by oxidative stress which is known to be the initial signal in this process of DNA damage [20]. When tested for genotoxicity few TCAs showed positive result and a few negative this was analysed and found the presence of an N atom at position 5 in the central ring of the positive compounds whereas the negative compounds were positioned with carbon at that position. And it was confirmed that the 5th position N in the central ring was responsible for the genotoxicity in case of TCAs [21]. Most of the antidepressants fall to this category with the presence of an N atom at the 5th position of the heterocyclic seven-membered ring that is known to have the genotoxic property. The above analysis is been proved by this study which shows the coincidence with the genotoxic findings in Drosophila produced by chemicals closely related to imipramine (clomipramine, lofepramine, and mianserin) [22]. Besides the N atom it was also reported that the aromatic ring might also prove dangerously related to mutagenic and carcinogenic events, it was reported that the structure might be the cause for the SCE with might be alternate to N atom. Recent papers also show that desipramine is also a potent inducer of genotoxicity and proved its positivity when cultured in C6 rat glioma cells [23].

3.2. Antipsychotics

Drug chlorpromazine possesses the adverse effect of mutagenic activity where the results are been reported by a few authors and it is also been studied in correlation with that of induction of mutagenesis in *S. Typhimurium* by photo-activated chlorpromazine [24]. It was suggested that in the tester strains the observed mutagenesis could have been induced during the repair processes of the DNA-induced lesions by chlorpromazine [19]. It was found that Phenothiazine and its derivatives used as pharmaceuticals lack the genotoxic effect in few of the standard mutagenic tests and hence it was evaluated for the further studies to check the genotoxic effect and its outcomes. Since phenothiazine derivatives are the most prescribed drugs it was found that they elevate the levels of chromosome aberrations whereas in other antipsychotics the frequency of prescription was too low and the patient numbers were too small, hence the exact conclusions made by few authors are unequivocal, but chlorinated phenothiazines and its derivatives showed Photomutagenic properties which were established in a most of the investigations made [25]. Phenothiazine and few other antipsychotics led to the decrease in the number of mutant colonies of strain TA98 that are exposed to benzpyrene type of mutagen. This was assessed when the above activity was found to compete

for the cytochrome P450 biding sites [26, 27]. When chlorpromazine was exposed to the mammalian cells in combination with the methotrexate or fluorodeoxyuridine it was found to increase the number of DNA single-strand breaks [28]. It was suggested that the interaction with calmodulin was responsible for it. The entrapment of the triplet oxygen by the chlorpromazine triple excited state leads to the formation of sulfoxide (oxidative activation). The most relevant free radical that cause the maximum effect was found to be the dechlorinated free radical (= promazine radical). The alternative reaction may include the following pathways of Formation of Promazine, dimerisation, or covalent linkage with the other molecules [25]. Few authors like Suryanarayana et al. [24] reported a positive effect of Trifluoperazine in the MNT (micronuclei test) test in mouse bone marrow and the CA test with mouse spermatocytes (increase in sex univalents and polyploids, only). Whereas Rao and Rao [29] showed a positive result for Fluphenazine. Siva Sankar and Geisler [30] observed in mouse leukocytes a doubling of centromere disjunction (the description of this aberration and the high spontaneous rate of occurrence (26%) suggests the possibility of staining artefacts).

4. CONCLUSION

In this review, we have explored the genotoxic effect of the few of the CNS drugs that are majorly characterized as antidepressants and antipsychotics. Few studies have shown that major antidepressants like fluoxetine, sertraline, clomipramine show extensive toxic activity when compared to other antidepressants lofepramine, mianserin etc. whereas antipsychotic agents like chlorpromazine, Phenothiazine is also known to possess the toxic effect on genetic material. This review also gives the idea of the mechanism of how the drug causes the genotoxic effect. These effects can be controlled by limiting the use of these drugs and switching to alternative drugs which have less or no toxic effect.

5. ACKNOWLEDGEMENT

Authors are very much thankful to Mrs Kusu Susan Cyriac assistant professor, Department of pharmacology, Karnataka College of Pharmacy, Bangalore. For their constant help and support.

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