

Cytotoxic effects of antipsychotic drugs implicate cholesterol homeostasis as a novel chemotherapeutic target

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The reported reduction in cancer risk in those suffering from schizophrenia may be because antipsychotic medications have antineoplastic effects. In this study, 6 antipsychotic agents with a range of structural and pharmacological properties (reserpine, chlorpromazine, haloperidol, pimozide, risperidone and olanzapine), were screened for their effect on the viability of cell lines derived from lymphoblastoma, neuroblastoma, non-small cell lung cancer and breast adenocarcinoma. We aimed to determine if antipsychotic drugs in general possess cancer-specific cytotoxic potential, and whether it can be attributed to a common mode of action. With the exception of risperidone, all drugs tested displayed selective inhibition of the viability of cancer cell lines compared with normal cells. Using Affymetrix expression microarrays and quantitative real-time polymerase chain reaction, we found that for the antipsychotic drugs, olanzapine and pimozide, cytotoxicity appeared to be mediated via effects on cholesterol homeostasis. The role of cholesterol metabolism in the selective cytotoxicity of these drugs was supported by demonstration of their increased lethality when coadministered with a cholesterol synthesis inhibitor, mevastatin. Also, pimozide and olanzapine showed accelerating cytotoxic effects from 12 to 48 hr in time course studies, mirroring the time-dependent onset of cytotoxicity induced by the amphiphile, U18666A. On the basis of these results, we concluded that the Class II cationic amphiphilic properties of antipsychotic drugs contribute to their cytotoxic effects by acting on cholesterol homeostasis and altering the biophysical properties of cellular membranes, and that drugs affecting membrane-related cholesterol pathways warrant further investigation as potential augmentors of standard cancer chemotherapy.

Although the overall prevalence of medical comorbidity in patients with schizophrenia is high,^{1,2} it has long been suggested that this group may have a reduced incidence of can-

cer compared with the general population.^{3,4} Many epidemiological studies have been conducted to investigate this possible link but cancer risk in schizophrenic patients remains a controversial issue.^{5,6} Nonetheless, a recent meta-analysis found that the pooled overall cancer incidence rates for patients with schizophrenia did not parallel their cancer risk factor exposure.⁷ The cause of this apparent reduction in cancer risk remains elusive. Genetic factors and the possibility of reduced cancer detection in patients have been considered,⁷ and antipsychotic drugs have been suggested as possible mediators of this effect.^{8,9}

Although antipsychotic drugs have chemically diverse structures and receptor affinity profiles, all interfere with dopaminergic transmission, which is believed to underlie their effects in reducing "positive" symptoms (e.g., delusions and hallucinations) of schizophrenia.^{10,11} The therapeutic effects of the "first generation" of synthetic antipsychotics are in direct proportion to their level of dopamine D2 receptor (D2R) antagonist action,¹² as is their propensity to cause extrapyramidal side effects and hyperprolactinemia.

Second generation antipsychotics, such as risperidone and olanzapine, were introduced in the 1990s and their antipsychotic efficacy is associated with a much lower risk of extrapyramidal side effects than first generation antipsychotics. However, they appear to induce greater metabolic adverse

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Abbreviations: D2R: dopamine D2 receptor; HMGCR: 3-hydroxy-3-methylglutaryl coenzyme A reductase; HMGCS1: 3-hydroxy-3-methylglutaryl-coenzyme A synthase-1; IC₅₀: 50% (cell viability) inhibiting concentration; Insig-1: insulin-induced gene-1; Insig-2: insulin-induced gene-2; LD50: 50% lethal dose; LDLR: low-density lipoprotein receptor; NSCLC: non-small cell lung cancer; qRT-PCR: quantitative real-time polymerase chain reaction; SC5DL: sterol-C5-desaturase like; SCAP: SREBP cleavage activating protein; SREBP: sterol-regulator element binding protein

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