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Interactions Between Hyperglycaemia, Drug Metabolism, and Toxicity Profiles: A Systems Biology Review

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ABSTRACT

Hyperglycaemia, a defining feature of diabetes mellitus and metabolic syndrome, exerts profound and multifaceted effects on drug metabolism, pharmacokinetics, and toxicity. These effects stem from coordinated disruptions in metabolic pathways, redox homeostasis, immune function, mitochondrial biology, and organ physiology. As global diabetes prevalence continues to rise, the overlap between chronic hyperglycaemia and therapeutic exposure has become a growing challenge in clinical pharmacology and toxicology. This review synthesizes systems-level insights into how hyperglycaemia modulates drug absorption, distribution, metabolism, and excretion (ADME), and how these changes modify susceptibility to adverse drug reactions (ADRs). We examine the cellular and molecular mechanisms through which elevated glucose alters enzymatic activity, transporter function, oxidative stress responses, inflammatory tone, and xenobiotic biotransformation. Organ-specific vulnerabilities in the liver, kidney, cardiovascular system, and immune system are explored, alongside emerging evidence from pharmacogenomics and exposomics. We also discuss the implications for dose optimization, therapeutic monitoring, drug–disease interactions, and precision medicine. A systems biology perspective reveals that hyperglycaemia not only modifies individual metabolic pathways but reconfigures entire regulatory networks, reshaping the toxicity landscape for numerous drug classes. Understanding these complex interactions is essential for improving drug safety, reducing treatment failures, and designing next-generation therapeutics for populations affected by chronic metabolic disease.

Keywords: Hyperglycaemia, drug metabolism, toxicity, systems biology, diabetes

INTRODUCTION

Chronic hyperglycaemia is no longer viewed solely as a biochemical aberration of glucose regulation; instead, it is recognized as a systemic metabolic disturbance with widespread consequences for cellular function, organ physiology, and pharmacological responses [1-6]. Diabetes mellitus, characterized by persistent elevation of circulating glucose, affects more than half a billion individuals globally, and its prevalence continues to climb [7-12]. The condition is associated with oxidative stress, chronic inflammation, endothelial dysfunction, altered lipid metabolism, and profound remodeling of metabolic and signaling networks. These pathological changes extend into the domain of drug metabolism and toxicity [13-17]. Patients with diabetes often require multiple long-term medications, including antihypertensives, lipid-lowering agents, antidiabetic drugs, and therapies for comorbidities such as infections or cardiovascular disease [18-24]. Hyperglycaemia and insulin resistance can significantly modify pharmacokinetic and pharmacodynamic profiles through their effects on CYP450 enzymes, phase II conjugation pathways, drug transporters, tissue perfusion, and renal elimination mechanisms [25-29]. These alterations contribute to increased variability in therapeutic response and heightened susceptibility to adverse drug reactions.

A systems biology framework is essential to fully understand these interdependencies [30-37]. Rather than acting through a singular mechanism, hyperglycaemia produces a cascade of interconnected perturbations-such as mitochondrial dysfunction, AGE formation, redox imbalance, inflammatory activation, and epigenetic remodeling-that converge on the pathways governing xenobiotic biotransformation [38-43]. This review explores the mechanistic foundations, organ-specific consequences, and clinical implications of hyperglycaemia–drug interactions, aiming to guide improved therapeutic strategies and risk assessment in individuals with metabolic disease [44-50].

2. Molecular and Cellular Effects of Hyperglycaemia Relevant to Drug Metabolism

2.1 Oxidative stress and redox imbalance

Hyperglycaemia is a potent driver of oxidative stress, exerting multifaceted effects on cellular metabolism and drug metabolism pathways [51-54]. Elevated intracellular glucose overwhelms the mitochondrial electron transport chain, causing electrons to leak from complexes I and III and generate superoxide [55-59]. Additional ROS are produced via glucose autooxidation, polyol pathway flux, and the non-enzymatic formation of advanced glycation end-products (AGEs). These reactive species not only damage lipids, proteins, and DNA but also directly impact the function and expression of drug-metabolizing enzymes [60-66]. Many cytochrome P450 (CYP450) isoforms are highly redox-sensitive; excessive ROS can suppress their transcription, destabilize protein folding, or reduce catalytic activity [60-66]. Persistent oxidative stress also depletes cellular glutathione, a central cofactor for phase II detoxification reactions such as glutathione conjugation. As a result, both phase I and phase II metabolism can be impaired, increasing susceptibility to drug accumulation and toxicity [13].

2.2 AGE–RAGE signaling and inflammation

Chronic hyperglycaemia promotes the accumulation of AGEs, which arise from non-enzymatic glycation of proteins, lipids, and nucleic acids [14]. AGEs interact with the receptor for advanced glycation end-products (RAGE), triggering NF-κB activation and sustained production of pro-inflammatory cytokines [15]. This low-grade chronic inflammation exerts downstream regulatory effects on drug metabolism, including downregulation of key CYP450 enzymes such as CYP3A4, CYP2C9, and CYP1A2[16]. By shifting the balance between pro- and anti-inflammatory mediators, AGE–RAGE signaling indirectly modulates the liver's capacity to metabolize xenobiotics, contributing to altered drug clearance and heightened toxicity risk.

2.3 Altered cellular energy metabolism

Insulin resistance and impaired glucose uptake force cells to rely more heavily on fatty acid oxidation rather than glucose oxidation [17]. This metabolic remodeling reduces NADPH availability, which is essential for reductive reactions in CYP450-mediated phase I metabolism. It also modifies the activity of key metabolic regulators such as PPARs, AMPK, and SREBP, reshaping the liver's adaptive responses to xenobiotic exposure [18]. Consequently, both the efficiency and the selectivity of drug metabolism are altered.

2.4 Epigenetic regulation and transcriptional remodeling

Hyperglycaemia induces persistent epigenetic changes, including DNA methylation, histone acetylation alterations, and microRNA dysregulation [19]. These modifications constitute a form of metabolic memory, meaning that even after glycaemic normalization, the transcriptional landscape of metabolizing enzymes remains altered [20]. Genes encoding CYP450 isoforms, conjugating enzymes, and nuclear receptors such as CAR and PXR are particularly affected, leading to long-term shifts in drug-processing capacity and variable susceptibility to adverse drug reactions [21].

3. Impact on Drug Absorption, Distribution, Metabolism, and Excretion

3.1 Absorption

Hyperglycaemia can substantially alter the gastrointestinal environment, affecting the absorption of orally administered drugs [22]. One major factor is diabetic gastroparesis, a condition characterized by delayed gastric emptying due to autonomic neuropathy. Slower gastric transit prolongs drug dissolution and delays the time to peak plasma concentration, which may reduce therapeutic efficacy or increase variability in pharmacodynamic responses [23]. In addition, elevated glucose levels affect the expression and function of intestinal transporters, including P-glycoprotein and various solute carrier (SLC) proteins, which play critical roles in the uptake and efflux of xenobiotics [24]. Hyperglycaemia also disrupts tight junction integrity between enterocytes, potentially increasing paracellular permeability for hydrophilic compounds [25]. Mucosal blood flow may be impaired due to microvascular dysfunction, further reducing the efficiency of nutrient and drug absorption. Collectively, these changes can lead to unpredictable bioavailability, particularly for drugs with narrow therapeutic windows or poor solubility [26].

3.2 Distribution

Alterations in plasma protein levels and microvascular perfusion significantly impact drug distribution in diabetic individuals [27]. Glycation of plasma albumin reduces its binding affinity for many highly protein-bound drugs, increasing the free, pharmacologically active fraction and potentially enhancing both efficacy and toxicity. In some cases, chronic hyperglycaemia can also reduce overall albumin levels through urinary losses in diabetic nephropathy, amplifying these effects [28]. Microvascular dysfunction further compromises tissue perfusion, limiting drug delivery to peripheral organs and modifying interstitial drug concentrations. These distribution changes are particularly relevant for lipophilic compounds and drugs targeting tissues with limited vascular supply.

3.3 Metabolism

The liver, as the primary site of drug metabolism, is profoundly affected by hyperglycaemia. Chronic elevated glucose and associated oxidative stress can downregulate multiple CYP450 isoforms, including CYP3A4, CYP2C9, and CYP1A2, though some isoforms may be upregulated depending on inflammatory status and disease stage [29]. Phase II reactions, such as glucuronidation, sulfation, and glutathione conjugation, are also impaired due to cofactor depletion and oxidative damage. Nuclear receptor signaling pathways, including CAR, PXR, and PPARs, may be modulated by hyperglycaemia, altering transcriptional control over metabolizing enzymes and further affecting drug clearance.

3.4 Excretion

Renal drug excretion is similarly altered in diabetes. Early in the disease, hyperfiltration may transiently increase clearance of some drugs, whereas progressive nephropathy reduces glomerular filtration, tubular secretion, and expression of transporters, necessitating careful dose adjustments [30]. Hyperglycaemia-driven oxidative injury and inflammation sensitize renal tubules to drug-induced nephrotoxicity, particularly from aminoglycosides, NSAIDs, and chemotherapeutic agents. These combined effects underscore the need for vigilant monitoring of drug levels and kidney function in diabetic patients.

4. Hyperglycaemia–Drug Class Interactions

4.1 Cardiovascular drugs

Hyperglycaemia significantly affects the pharmacokinetics and pharmacodynamics of cardiovascular agents. Beta-blockers, ACE inhibitors, and angiotensin receptor blockers may demonstrate altered absorption, distribution, or hepatic metabolism in individuals with diabetes [31]. Reduced microvascular perfusion and glycation of plasma proteins can modify tissue drug concentrations, potentially diminishing therapeutic efficacy. Statins, widely used for lipid management, carry an increased risk of myopathy in diabetic patients. This is partly due to hyperglycaemia-induced mitochondrial dysfunction in skeletal muscle, impaired glucose utilization, and increased oxidative stress, which exacerbate muscle injury [32]. Furthermore, diabetes-related inflammation may alter statin metabolism through modulation of CYP3A4 activity, affecting systemic exposure and toxicity risk.

4.2 Antimicrobial drugs

Diabetes alters both the pharmacokinetics and pharmacodynamics of antimicrobial agents. Aminoglycosides, vancomycin, and certain antifungals show higher nephrotoxic or ototoxic potential in hyperglycaemic individuals due to compromised renal function and oxidative stress in tubular cells [33]. Tissue penetration of antibiotics may be reduced in poorly perfused or inflamed diabetic tissues, decreasing antimicrobial efficacy. At the same time, hyperglycaemia promotes microbial growth and impairs innate and adaptive immune responses, creating an environment in which infections are more severe and treatment-resistant.

4.3 Anticancer agents

Many chemotherapeutics exert cytotoxicity via ROS-mediated mechanisms. In hyperglycaemic conditions, basal oxidative stress is elevated, which can both potentiate anti-cancer efficacy and increase collateral toxicity in non-malignant tissues [34]. Diabetes impairs DNA repair pathways, enhancing susceptibility to genotoxic damage from alkylating agents, platinum compounds, and topoisomerase inhibitors [35]. Altered drug metabolism and reduced detoxification capacity further elevate the risk of systemic and organ-specific toxicity.

4.4 CNS drugs

Central nervous system drugs are also affected by hyperglycaemia. Diabetes-induced changes in blood–brain barrier permeability, chronic neuroinflammation, and oxidative stress can modify drug distribution, clearance, and receptor sensitivity [36]. Antidepressants, anticonvulsants, and antipsychotics may exhibit altered efficacy and heightened adverse effects. Sedation, cognitive impairment, and neurotoxicity are more likely, necessitating careful monitoring and individualized dosing.

CONCLUSION

Hyperglycaemia exerts extensive, systems-level influences on drug disposition and toxicity. By reshaping metabolic, inflammatory, mitochondrial, and epigenetic networks, elevated glucose alters the activity of drug-metabolizing enzymes, drug transporters, and organ vulnerabilities. These changes heighten the risk of adverse drug reactions and complicate therapeutic decision-making for millions of individuals living with diabetes. A systems biology framework is essential to capture the complexity of these interactions, enabling individualized treatment strategies and improved safety outcomes. Continued integration of multi-omics data, computational modeling, and mechanistic experimentation will advance precision medicine approaches capable of accounting for the dynamic interplay between metabolic disease and pharmacological exposure.

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