Pulmonary hypertension associated with diazoxide: the SUR1 paradox

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The activation of SUR1 and SUR2 is beneficial in experimental models of PH. Paradoxically, the SUR1 activator, diazoxide, leads to cases of PAH in children. Further investigation is needed. https://bit.ly/462KdG7

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Abstract

The ATP-sensitive potassium channels and their regulatory subunits, sulfonylurea receptor 1 (SUR1/Kir6.2) and SUR2/Kir6.1, contribute to the pathophysiology of pulmonary hypertension (PH). Loss-of-function pathogenic variants in the *ABCC8* gene, which encodes for SUR1, have been associated with heritable pulmonary arterial hypertension. Conversely, activation of SUR1 and SUR2 leads to the relaxation of pulmonary arteries and reduces cell proliferation and migration. Diazoxide, a SUR1 activator, has been shown to alleviate experimental PH, suggesting its potential as a therapeutic option. However, there are paradoxical reports of diazoxide-induced PH in infants. This review explores the role of SUR1/2 in the pathophysiology of PH and the contradictory effects of diazoxide on the pulmonary vascular bed. Additionally, we conducted a comprehensive literature review of cases of diazoxide-associated PH and analysed data from the World Health Organization pharmacovigilance database (VigiBase). Significant disproportionality signals link diazoxide to PH, while no other SUR activators have been connected with pulmonary vascular disease. Diazoxide-associated PH seems to be dose-dependent and potentially related to acute effects on the pulmonary vascular bed. Further research is required to decipher the differing pulmonary vascular consequences of diazoxide in different age populations and experimental models.

Introduction

Intracellular nucleotides gate ATP-sensitive potassium channels (K_{ATP}), which are composed of inward-rectifier K^+ channel (Kir6.x) and sulfonylurea receptor (SUR) subunits. Diazoxide, a potassium channel opener, is known to activate both SUR1 and SUR2 [1]. While SUR1 is primarily found in pancreatic β-cells, SUR2 is mainly expressed in the cardiovascular system and smooth muscle. The activation of the first by diazoxide has been found to inhibit insulin release, while the activation of the latter leads to vasodilation and decreased blood pressure, thus rendering it a valid therapeutic option for the treatment of certain forms of hypoglycaemia as well as hypertension. In recent years, reports have emerged linking diazoxide treatment to pulmonary hypertension (PH) in infants treated with diazoxide for neonatal hypoglycaemia or hypoglycaemia complicating other diseases [2–5]. This has been a paradoxical finding, since the activation of SUR1 and SUR2 channels improved haemodynamic and pulmonary vascular remodelling in experimental models of PH [6]. Interestingly, loss-of-function pathogenic variants in the *ABCC8* gene, which encodes SUR1, were found to be responsible for heritable pulmonary arterial hypertension (PAH) [7]. In this study, our objective was to discuss the role of SUR1 and SUR2 proteins in

the pathophysiology of PH, as well as the beneficial effects of diazoxide in experimental PH models. Additionally, we analysed the seemingly contradictory association between diazoxide and the occurrence of PH in infants, by analysing case studies from the literature and data from the World Health Organization (WHO) pharmacovigilance database (VigiBase).

Role of SUR1 and SUR2 in pathophysiology in PAH

ATP-sensitive potassium channels

K_{ATP} is a hetero-octameric complex constituted by four inward-rectifier-K^+ channel subunits (Kir6.x), that make up the pore and four regulatory subunits composed of SUR subunits (SUR.x), which belong to the ATP-binding cassette (ABC) transporter superfamily. SUR is a large subunit that binds sulfonylureas and ATP. K_{ATP} channel activation occurs through a reduction in intracellular ATP concentrations or an increase in nucleotide-diphosphate concentrations [8]. There are three SUR isoforms: SUR1, SUR2A and SUR2B, with SUR1 and SUR2 having ~70% homology [1, 8]. The K_{ATP} subunit can co-assemble differently, depending on the tissue. For instance, SUR1 is mainly expressed in pancreatic β-cells associated with Kir6.2, while SUR1 also associates with Kir6.2 in the pulmonary circulation, and it has been proposed that SUR1 activation could be used for the treatment of PAH [7, 9]. SUR2A is mainly described to be expressed in cardiac and skeletal muscles while SUR2B is expressed ubiquitously [1]. In humans, *ABCC8* encodes SUR1, *ABCC9* encodes SUR2 (which can be alternatively spliced into two isoforms, SUR2A or SUR2B), *KCNJ11* encodes Kir6.2 and *KCNJ8* encodes Kir6.1 [10]. The SUR2A/Kir6.2 channel is typically considered the cardiac K_{ATP} channel, whereas both SUR2A/Kir6.1 and SUR2B/Kir6.2 are generally considered to be vascular K_{ATP} channels. Transcripts for SUR2B and Kir6.1 are present in both rat and human pulmonary artery smooth muscle cells (hPASMCs) [11]. The lungs, human pulmonary artery endothelial cells (hPAECs) and hPASMCs in both controls and PAH patients, as well as in rat models of PH, contain SUR2A, SUR2B and Kir6.1 proteins [6, 9].

SUR1/Kir6.2 in pulmonary hypertension

The expression of SUR1 and Kir6.2 is comparable in hPAECs and hPASMCs from PAH patients and in experimental PH models. SUR1 activation reduces the proliferation rate of control hPAECs and hPASMCs, but does not affect the proliferation rate of hPAECs and hPASMCs derived from idiopathic PAH patients [8, 9]. Because diazoxide had several side-effects, we used two additional SUR1 activators: VU0071063 and NN414. These two additional compounds have superior selectivity for SUR1/Kir6.2 channels, explaining why both molecules have been recently proposed for replacing diazoxide and treating congenital hyperinsulinism [12]. *Ex vivo* experiments testing three different SUR1 activators (diazoxide, VU0071063 and NN414) on pulmonary artery relaxation in control and PH conditions demonstrated that SUR1 activation mediated relaxation of pulmonary arteries, while pharmacological inhibition of the SUR1/Kir6.2 channel led to increased constriction of pulmonary arteries [9]. These findings suggest that SUR1 activation can modulate the proliferation of specific cell types involved in PH, providing potential insights into targeted therapeutic strategies for PAH. Diazoxide therapy decreased right ventricle systolic pressure and alleviated pulmonary vessel neomuscularisation in preventive and curative approaches in PH induced by monocrotaline or chronic hypoxia in rats. Chronic exposure of control rats to diazoxide did not result in any cardiovascular effects. Diazoxide is described to have several effects beyond acting as a SUR1/Kir6.2 channel opener, including activation of SUR2, modulation of additional ion channels and ATPase functions, and direct action on mitochondrial functions [9, 13, 14]. These SUR1/Kir6.2 diazoxide effects could partly explain why some infants treated with diazoxide for neonatal hypoglycaemia or hypoglycaemia developed PH.

Contrary to diazoxide and VU0071063, NN414 does not act directly on mitochondria [13, 15, 16]. Moreover, NN414 is 100-fold more potent selective agonist than diazoxide for SUR1/Kir6.2 channels [15]. Thus, we focused on NN414 for our *in vivo* experiments, demonstrating that administering NN414 therapy from day 14 to 21 after monocrotaline exposure led to improvements in several PH-related parameters. These improvements encompassed right ventricular systolic pressure, cardiac output, pulmonary vascular resistance and the Fulton index, along with a reduction in the number of muscularised pulmonary vessels [9]. Taken together, these findings suggest that *in vivo* activation of SUR1 using two different activators, diazoxide and NN414, has the potential to reduce the severity of PH in experimental models (figure 1).

SUR2/Kir6.1 in pulmonary hypertension

SUR2A, SUR2B and Kir6.1 are expressed in the lungs of both controls and patients with PAH, as well as in the monocrotaline PH rat model [6]. Activation of SUR2 with pinacidil caused relaxation of pulmonary arteries in both rats and humans and resulted in reduced cell proliferation and migration in hPASMCs and hPAECs from controls and PAH patients. Additionally, patch-clamp experiments on rat right ventricular cardiomyocytes showed that SUR2 activation reduced the action potential duration of the right ventricle.

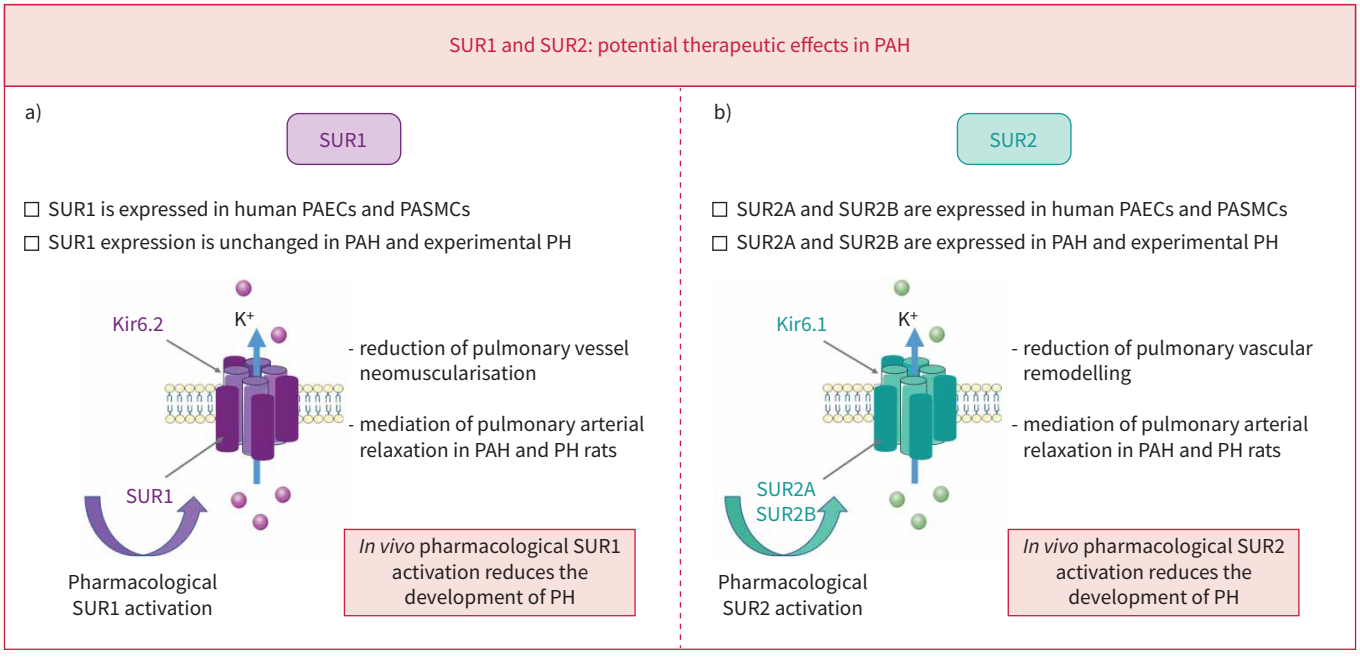

FIGURE 1 Potential beneficial effects of sulfonylurea receptor (SUR)1 and SUR2 activation in the pathophysiology of pulmonary hypertension (PH). a) SUR1 is expressed by human pulmonary artery endothelial cells (PAECs) and pulmonary artery smooth muscle cells (PASMCs). In the pulmonary arterial hypertension (PAH) and experimental PH context, SUR1 expression is unchanged compared to the control condition. Pharmacological activation of SUR1 by two different compounds (diazoxide and NN414) mediated pulmonary arterial relaxation, reduced pulmonary vessel neomuscularisation and reduced the development of experimental PH. b) Both human PAECs and PASMCs express SUR2A and SUR2B. In the PAH and experimental PH context, SUR2A and SUR2B are still expressed compared to the control condition. Pharmacological activation of SUR2A or SUR2B by pinacidil compound mediated pulmonary arterial relaxation, reduced pulmonary vascular remodelling and reduced the development of experimental PH.

This result indicates that SUR2 activation affects the electrophysiology of right ventricular cardiomyocytes, which is crucial in the context of PH. Further investigation into how SUR2 activation influences the action potential duration may highlight potential therapeutic options for managing right ventricular dysfunction associated with PH. Improvements in PH were observed after SUR2 activation in monocrotaline and chronic hypoxia PH models [6]. These results suggest that SUR2A, SUR2B and Kir6.1 are present in hPASMCs and hPAECs of both healthy individuals and those with PAH, and that *in vivo* SUR2 activation could be a potential therapeutic option for PAH.

Pharmacology of diazoxide

A variety of drugs can either stimulate or inhibit K_{ATP} channels by binding to SUR (table 1). The K^+ channel openers pinacidil, nicorandil and diazoxide are known to stimulate native K_{ATP} channels. Given

TABLE 1 Sulfonylurea receptor (SUR)1 and SUR2 activators and inhibitors

SUR1 and SUR2 activators	SUR1 and SUR2 inhibitors
Pinacidil	Tolbutamide
Nicorandil#	Glibenclamide
Diazoxide	Acetohexamide
Cromakalim	Tolazamide
Minoxidil#	Glipizide
	Chlorpropamide
	Glyburide

Information from DrugBank [17] and the International Union of Basic and Clinical Pharmacology [18]. #: SUR activators with additional vasodilator properties were identified.

the different expression of SUR subtypes in tissues (*i.e.* pancreatic SUR1, cardiac SUR2A and smooth muscle SUR2B), they display heterogeneous sensitivity to drugs. Indeed, diazoxide stimulates the pancreatic β-cell K_{ATP} channels and the smooth muscle K_{ATP} channels, but not the cardiac K_{ATP} channels. In contrast, nicorandil or cromakalim activate cardiac K_{ATP} channels and the smooth muscle K_{ATP} channels, but not the pancreatic β-cell K_{ATP} channels [19].

Diazoxide is a nondiuretic sulfonamide of the benzothiazine family used to treat hyperinsulinaemic hypoglycaemia through inhibition of insulin release. This drug can be used in infants, children and adults. Recommended dosages are 5–10 $mg \cdot kg^{-1}$ per day (up to 15 $mg \cdot kg^{-1}$ per day in infants and young children) in twice or thrice daily intake with a progressive titration. Difference in dosages is mainly due to pharmacokinetic and pharmacodynamic changes during development responsible for age-related differences in drug disposition. This includes gastric pH, maturity of cytochrome P450 isoforms and single glucuronosyltransferase, apparent volume of distribution, concentration of plasma proteins, glomerular filtration rate and active tubular secretion [20]. Available data from the product drug characteristics indicate that intake dose is quickly absorbed, and highly bound to plasma proteins (>90%). The elimination half-life after oral administration is between 24 and 36 h in adults. It is shorter in young children (9.5–24 h). Its urinary excretion by glomerular filtration is essentially in the nonmetabolised form. Kizu *et al.* [21] presented a population pharmacokinetic model for diazoxide in children with hyperinsulinaemic hypoglycaemia, utilising a one-compartment model derived from 22 Japanese patients. The study found that both oral clearance and the volume of distribution were proportionate to bodyweight, with the notable finding that oral clearance in females was 39% higher than that in males [21]. The estimated interindividual variability in oral clearance and volume of distribution was 37.9% and 49.3%, respectively. Steady-state concentrations of diazoxide were similar following twice and three times daily dosing when the total daily doses were comparable. The potential risk of diabetes mellitus and/or hyperglycaemia increases when serum concentrations of diazoxide exceed 100 $\mu g \cdot mL^{-1}$, suggesting dose-related diazoxide side-effects [21]. Beyond hypotension, the cardiovascular safety profile of diazoxide is characterised by transient episodes of myocardial ischaemia manifesting most often as angina, cardiac arrhythmias and occasionally myocardial infarction [22, 23]. Moreover, pericardial effusion, cardiomyopathy and congestive heart failure have been reported with prolonged exposure to diazoxide [24].

Beneficial effects of diazoxide in animal models of PH

Diazoxide exhibits more potent agonistic effects on SUR1, while acting as a weaker activator on SUR2. In contrast, pinacidil shows higher selectivity towards SUR2. Through experiments conducted using excised inside-out patches, D'hahan *et al.* [25] observed that diazoxide led to a five-fold increase in SUR1/Kir6.2 currents, while having only minor effects on SUR2A/Kir6.2 currents. The SUR1/Kir6.2 and SUR2/Kir6.2 channels display differences in sulfonylurea sensitivity to diazoxide [26–28]. Babenko *et al.* [26] utilised chimeric human SUR1-SUR2A/Kir6.2 channels and discovered that the sensitivity of SUR2 to pinacidil is conferred by the transmembrane domain 12–17 of SUR2. In contrast, the sensitivity of SUR1 to diazoxide is conferred by the transmembrane domain 6–11 of SUR1, suggesting that diazoxide primarily acts on SUR1, as compared to SUR2. The effects of diazoxide on SUR1/Kir6.2, SUR2A/Kir6.2 or SUR2B/Kir6.2 channels depend on the cytosolic ADP levels [29]. Precisely when the intracellular ADP concentration is low, diazoxide strongly activates channels containing SUR1 or SUR2B. Activation of Kir6.2/SUR2A (cardiac K_{ATP} channel) by diazoxide is observed only at an elevated ADP concentration (100 $\mu mol \cdot L^{-1}$) [25]. Our recent study showed that *in vivo* diazoxide treatment reduces experimental PH development [9]. While we cannot entirely rule out the possibility that this reduction in PH is partially attributed to the activation of SUR2 channels, we obtained comparable results using NN414, a highly potent molecule that selectively targets SUR1. This finding confirms that targeting SUR1 might be a novel therapeutic option in the management of PAH [9].

Heritable PAH in *ABCC8* pathogenic variant carriers

The *ABCC8* (*ATP-binding cassette subfamily C member 8*) gene encodes the SUR1 protein. Bohnen *et al.* [7] identified a *de novo* missense variant (c.G2873A, p.R958H) in the *ABCC8* gene through exome sequencing in a patient diagnosed with idiopathic PAH at the age of 10 years. Subsequent evaluation of rare or novel variants in the *ABCC8* gene in two cohorts (Columbia University and UK) revealed 11 additional heterozygous predicted damaging *ABCC8* variants. Of these, two had associated congenital heart disease, including large atrial septal defect and ventricular septal defect [7]. All individuals were heterozygous for these rare variants, consistent with the autosomal dominant inheritance of PAH. Alignment of the *ABCC8* gene sequence showed that all missense variants occurred at amino acid residues conserved across species and in critical domains. Five variants have been reported in patients with congenital hyperinsulinism while two variants have been reported in patients with transient or permanent neonatal diabetes mellitus.

Two large PAH cohorts from the United States (US) and Spain confirmed the involvement of *ABCC8* in PAH [30, 31]. In the US-PAH biobank including 2572 PAH cases with exome sequencing, predicted deleterious *ABCC8* missense variants were found in 28 patients [31]. Another study including panel gene sequencing of 624 PAH cases from the National Spanish PAH Registry identified seven additional variants in the *ABCC8* gene [30]. Liu *et al*. [32] reported an *ABCC8* pathogenic variant through exome sequencing in a newborn with persistent PH and hypoglycaemia.

Bohnen *et al*. [7] studied the SUR1 function in eight out of the 12 identified *ABCC8* variants putatively associated with PAH. They found that all tested *ABCC8* variants led to a loss of ATP-sensitive potassium channel function, and that the channel currents were potentially rescued by diazoxide *in vitro*. In addition, the study showed that *ABCC8* gene expression was higher in PAH patients with *BMPR2* pathogenic variants (the most frequent PAH predisposing gene) compared to healthy controls [10].

The *ABCC9* gene encodes the SUR2 protein, and gain-of-function mutations were associated with Cantu syndrome, a rare condition characterised by hypertrichosis, a distinctive facial appearance, osteochondroplasia, cardiac defects and pericardial effusion [33]. Rare cases of PH with complex and multiple mechanisms have been reported in Cantu syndrome [34–36]. However, *ABCC9* pathogenic variants were not identified in a large cohort of PAH patients. Further research is required to clarify the pathogenic mechanism and penetrance of *ABCC8* pathogenic variants in PAH.

Pulmonary hypertension associated with diazoxide

Analysis of case studies in the literature

We identified 31 individual case reports and three series that reported a total of 30 additional cases, resulting in 61 cases in total (supplementary table S1) [2–5, 37–47]. All cases occurred in infants aged <6 months treated with diazoxide for neonatal hypoglycaemia or hypoglycaemia complicating other diseases, including genetic diseases. Low birthweight, prematurity and/or congenital cardiovascular anomalies were common. Doses of diazoxide were generally >10 $mg \cdot kg^{-1}$ per day, but some cases of PH occurred in patients receiving lower doses of diazoxide (minimum 2 $mg \cdot kg^{-1}$ per day) [5]. The delay between the start of diazoxide therapy and the identification of PH varied significantly, with a range of 2–317 days, although the majority of cases presented within the first month of diazoxide initiation. Primary symptoms included respiratory distress and right heart failure, with more severe cases necessitating mechanical ventilation and two patient requiring veno–arterial extracorporeal membrane oxygenation [4, 38]. The diagnosis was based on echocardiographic abnormalities in almost all patients. Only two patients underwent right heart catheterisation, with one exhibiting severe isolated pre-capillary PH and the other presenting mixed pre- and post-capillary PH [39, 40]. Diazoxide therapy was discontinued for all patients, resulting in rapid improvements that included echographic normalisation in most cases, sometimes occurring within a month after cessation of the medication. Despite the implementation of extracorporeal membrane oxygenation, one patient succumbed to PH [4].

Estimating the prevalence of PH in patients exposed to diazoxide is challenging due to the inability to precisely determine the number of patients exposed worldwide. Furthermore, the lack of systematic confirmation through right heart catheterisation and the occasional spontaneous resolution after treatment cessation could lead to underreporting of diazoxide-associated PH cases. The study by Herrera *et al*. [48] represents the most comprehensive retrospective cohort study of children with hyperinsulinism treated with diazoxide over a 10-year period. During this period, 295 patients were included, and seven were diagnosed with PH following diazoxide initiation, corresponding to a prevalence of 2.4%. The frequency of PH was even higher in another retrospective study on 177 patients treated by diazoxide, in which 13 patients developed PH, diagnosed by TTE, corresponding to an incidence of 7% [2].

Analysis of the WHO pharmacovigilance database, VigiBase

We extracted and summarised all individual case safety reports of PAH and PH reported in the WHO pharmacovigilance database associated with diazoxide (only suspect cases) using the standardised medical query “pulmonary hypertension” (www.meddra.org). We then conducted a pharmacovigilance disproportionality analysis using the Bayesian neural network method, estimating the information component (IC). An IC_{LB} (lower boundary of the IC 95% credibility interval) >0 was deemed significant [49]. Disproportionality analyses quantify the extent to which a drug–event pair occurs “disproportionately” to what would be expected if there were no association between the drug and the event [50]. We performed two analyses using the standardised medical query “pulmonary hypertension” (narrow) and the preferred term “pulmonary arterial hypertension”. To investigate the role of SUR1 and SUR2 in the pathogenesis of PH related to diazoxide intake, we compared the disproportionality signals associated with SUR activators

to those associated with SUR inhibitors (table 1). The protocol of the study has been pre-registered on Open Science Framework (osf.io/mab93).

Among the 32 610 353 individual case safety reports entered in VigiBase in November 2022, 846 cases were reported with diazoxide, and 61 cases of PH since 1983 were identified by our search strategy: 43 PH, 14 PAH, three right ventricular failure, two right ventricular hypertrophy, two tricuspid valve incompetence, one pulmonary vein stenosis, one right ventricular dysfunction and one right atrial dilatation. 51% (31 out of 61) of patients were female and 82% (50 out of 61) were aged <2 years. 93% of cases were considered serious; two were fatal and five did not recover despite drug withdrawal (supplementary table S2). The median (interquartile range (IQR)) onset of PH after diazoxide introduction was 14.5 (5.8–34.8) days. Median (IQR) dose of diazoxide (available in 15 cases) was 10 (8.75–15.0) mg kg^{-1} per day. Diazoxide was withdrawn in 42 cases and PH had resolved at the time of reporting in 25 cases (not resolved in two cases and unknown for 15 cases). Causality assessment was performed in 18 cases by the reporter (Naranjo or WHO causality assessment system) and the role of diazoxide was considered possible in 16 cases and probable in two. Pharmacovigilance disproportionality signals were significant for diazoxide for PH (IC 5.16, 95% credibility interval (CrI) 4.77–5.51) and PAH (IC 4.10, 95% CrI 3.21–4.78). No other cases were reported for the other SUR activators pinacidil and cromakalim. When grouping with SUR activators displaying vasodilator properties (minoxidil and nicorandil), the signal decreased widely (IC 0.31, 95% CrI 0.02–0.59). No signal was found for SUR inhibitors (sulfonylureas) for PH or PAH (figure 2).

Although selective reporting and heterogeneity in case coding among countries represent inherent limitations of pharmacovigilance disproportionality analyses, these results suggest a higher reporting rate of pulmonary hypertension with diazoxide, compared to other SUR activators and inhibitors.

Mechanisms of pulmonary hypertension associated with diazoxide

Diazoxide showed cardioprotective effects in several species, including rats, rabbits, dogs and humans. *In vitro* experiments have used concentrations of 10–100 µmol·L^{-1}, while *in vivo* experiments have used doses of 1–10 mg·kg^{-1} intravenously [14, 51, 52]. Diazoxide can inhibit the succinate dehydrogenase, a mitochondrial complex II protein [53]. This inhibition also occurs in the heart, which partially accounts for the cardioprotective effects of diazoxide [54, 55].

Although diazoxide has other off-target effects, diazoxide could also inhibit voltage-gated K^+ and calcium (Ca^{2+}) channels [14]. Moreover, diazoxide could also induce mitochondrial membrane depolarisation, independently of SUR1 [56]. While the direct impact of diazoxide on ion channels in the cardiovascular

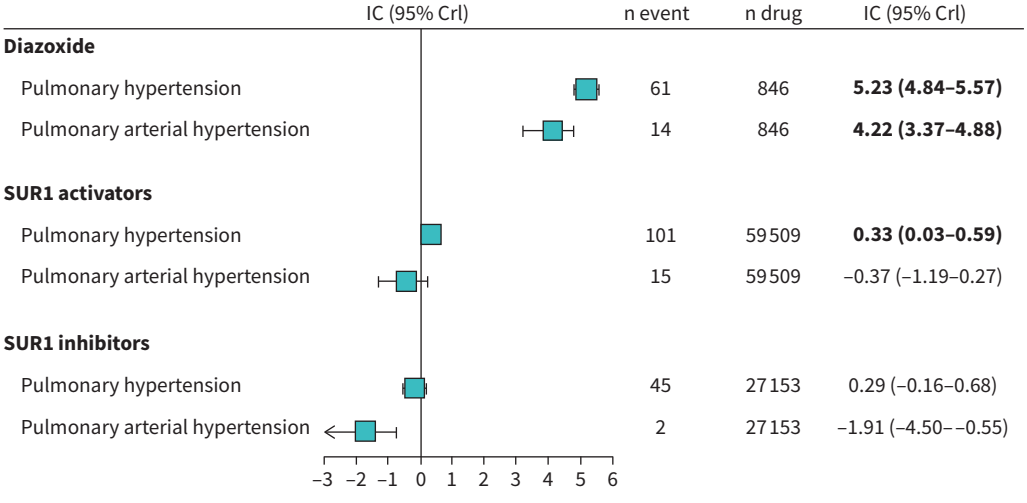

FIGURE 2 Results of the disproportionality analyses for pulmonary hypertension (standardised medical query, narrow) and pulmonary arterial hypertension (preferred term) for diazoxide alone, sulfonylurea receptor (SUR)1 activators (narrow: only pinacidil, cromakalim and diazoxide) and SUR1 inhibitors. Number of reported cases (n event), total number of cases reported for drugs or groups of drugs of interest (n drug) and information component (IC) values (95% credibility intervals (CrI)) are presented. Bold type represents statistical significance.

system has not been documented, it has been observed that in rat cerebral arterial smooth muscle cells, diazoxide-induced mitochondrial depolarisation results in the production of reactive oxygen species which could activate Ca^{2+} sparks, leading to large-conductance Ca^{2+}-activated K^+ channels, leading to vasodilation [57]. In contrast, reactive oxygen species production mediated by diazoxide could also activate voltage-gated K^+ channels resulting in vasodilation [56]. Further explorations are required to understand how diazoxide can exhibit both inhibitory and activating effects on different ion channels and how these diverse actions contribute to the overall physiological response, especially in the context of pulmonary vascular function.

Ohnishi *et al.* [40] reported a possible threshold effect in a child treated with diazoxide who exhibited no PH symptoms at a dose of 10.4 mg kg^{-1} per day, but developed PH when the diazoxide dosage was increased to 11.5 mg kg^{-1} per day. This report suggests that diazoxide dose influences toxicity more than duration of administration. In small-for-gestational-age infants with hyperinsulinaemic hypoglycaemia, data demonstrated the safety of low-dose diazoxide (3–5 mg kg^{-1} per day) in these patients [58]. These studies suggest that reducing the diazoxide dose could prevent the harmful development of PH in hyperglycaemic infants.

Diazoxide-associated PH is most often rapidly reversible, suggesting an acute effect on the pulmonary vascular bed, presumably through vasoconstriction. Nevertheless, identification of cases that are not fully reversible may imply an effect on pulmonary vascular remodelling directly related to diazoxide-dependent mechanisms or because of prolonged PH leading to irreversible pulmonary circulation abnormalities. The absence of invasive haemodynamic studies does not allow for conclusions about the risk factors and prevalence of residual PH. Persistent PH has also been noted in cases of PAH associated with dasatinib therapy, a tyrosine kinase inhibitor approved for the treatment of chronic myeloid leukaemia [59, 60]. Finally, we cannot rule out the possibility that the paradoxical effects of diazoxide (inducing PH in infants on the one hand and treating PH by activating SUR1 and SUR2 in animal models of PH on the other) may be related at least in part to age- and species-dependent differences in the pulmonary vascular bed as well as the baseline state of the pulmonary vessels at the time of diazoxide exposure (normal or with vascular remodelling).

Indeed, the occurrence of diazoxide-induced PH seems to contradict experimental data from animal models where SUR1/2 activators alleviate the disease and the identification of *ABCC8* loss-of-function variants in heritable PAH. Nevertheless, even if this seems paradoxical, it is not the only paradoxical situation in PAH. For instance, pathogenic variants in the *GDF2* gene, which encodes bone morphogenetic protein (BMP)9, predispose individuals to PAH, and administration of BMP9 can reverse established PH in animal models of the disease caused by BMP type II receptor deficiency [61]. In contrast, the lack of BMP9 in *Bmp9*$^{-/-}$ knockout mice or its suppression *via* neutralising anti-BMP9 antibodies substantially protect against chronic hypoxia-induced PH [62]. Furthermore, among drug-associated PAH, the potential beneficial effect on pulmonary vascular remodelling of certain tyrosine kinase inhibitors, like imatinib, is noteworthy, and has provided justification for clinical trials in PAH [63]. This is juxtaposed with the risk of PAH induced by other tyrosine kinase inhibitors such as dasatinib or bosutinib [64, 65]. Additionally, cyclophosphamide has been shown to induce pulmonary veno-occlusive disease lesions in experimental animal models and humans [66], despite being a standard treatment for PAH associated with certain connective tissue diseases such as systemic lupus erythematosus [67, 68]. These findings underscore the complex role of SUR1/2, which is likely to be intricate and could vary depending on the context, particularly the existence of a healthy or abnormal state of underlying pulmonary circulation. Of note, it is also plausible that diazoxide may induce PH *via* mechanisms that do not involve SUR1/2, thus highlighting the need for specific experimental investigations.

Conclusion

In conclusion, experimental data have shown an involvement of SUR1 and SUR2 in the pathophysiology of PAH, with a beneficial effect of SUR1 and SUR2 activation in animal models of PH. These findings are reinforced by the identification of loss-of-function pathogenic variants in the *ABCC8* gene, which encodes SUR1, in isolated PAH or PAH associated with congenital heart disease. Paradoxically, diazoxide, a SUR1 activator, has been associated with the occurrence of cases of PH in children treated for neonatal hypoglycaemia. This association was reinforced by the analysis of pharmacovigilance data showing a significant disproportionality signal for diazoxide, while no other SUR activators or inhibitors were associated with PAH. Deciphering the roles of SUR1 and SUR2 in PH, as well as the mechanisms of diazoxide-associated PH, requires further research and could significantly contribute to our understanding of PAH pathobiology.

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