Advances in the mechanism of action of metformin in pituitary tumors

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Abstract

Pituitary tumors are common intracranial tumors, but when faced with drug-resistant or aggressive tumors, existing medical measures may not provide good control, leading to progression and deterioration. Metformin, a traditional hypoglycemic drug, has been newly discovered to have multiple functions, including antitumor effects. There have been studies on the mechanism of metformin for the treatment of pituitary tumors, but it is uncertain whether it will provide new adjuvant or alternative therapies for the treatment of pituitary tumors. We analyzed the potential mechanisms of action of metformin on the inhibition of pituitary tumor growth and hormone secretion by reviewing the available literature.

INTRODUCTION

1. Introduction

Pituitary adenoma is a common intracranial tumor, accounting for approximately 10% to 15% of neurological tumors, and its incidence is second only to glioma and meningioma, ranking third among intracranial tumors\(^\text{[1-5]}\). Pituitary tumors originate in the anterior pituitary gland and are usually benign lesions with slow growth. They are classified according to their size: pituitary microadenomas (<1 cm in diameter), macroadenomas (≥1 cm in diameter) and giant adenomas (>4 cm in diameter).\(^\text{[6-7]}\) According to their different growth sites, they can secrete different hormones such as
GH, PRL, ACTH, TSH etc or they can be nonfunctional adenomas that do not secrete hormones. Clinical manifestations mainly include the occupational effect of the tumor and endocrine symptoms due to hyper- or hypofunction of the pituitary or target gland. Although most pituitary tumors can be controlled by drug therapy, surgery, and radiation therapy, some of these tumors may become drug resistant or recurrent, or even invade surrounding tissue structures, which may make treatment more difficult or prevent effective control of the tumor to achieve the desired therapeutic goals, so it is critical to find alternative therapies or new technologies to control the growth and hormone secretion of resistant or invasive pituitary tumors. Secretion is critical.

Metformin is a drug widely used in the treatment of diabetes mellitus. In addition to its ability to reduce liver damage, promote insulin production, and increase insulin sensitivity and peripheral glucose utilization for hypoglycemic effects. In recent years, a number of in vitro and in vivo studies and reviews have shown that metformin has the effect of inhibiting the growth of various types of tumors or cancers, including neuroendocrine tumors, through different ways in the different environment, which indicates that metformin may help to reduce the possibility of tumor or cancer occurrence and treatment in patients. Although there are some epidemiological data recording the relationship between metformin treatment and reducing the risk of patients suffering from multiple tumors or cancers, to confirm the role of metformin as a potential drug for preventing and treating multiple tumors or cancers, but information on the impact of metformin on pituitary tumor treatment is currently limited or not entirely certain. In this review, we review the available literature on the role of metformin in pituitary tumors and discuss the possible potential mechanisms of action of metformin in pituitary tumors.

2. Mechanism of action study

2.1 Mitochondria-mediated pathways

The Bcl-2 family is a key regulatory member of the mitochondrial-mediated apoptotic pathway, activating the downstream death program, which in turn leads to caspase-3 enzyme cleavage and ultimately apoptosis, characterized by a decrease in MMP.
In a study, a decrease in MMP, increased expression of pro-apoptotic proteins and decreased expression of anti-apoptotic proteins were observed in GH3 cells treated with metformin, again suggesting the involvement of the mitochondria-mediated apoptotic pathway, indicating that metformin may induce apoptosis in GH3 cells by downregulating the Bcl-2/BAX ratio and inducing caspase-3 cleavage activation and thus achieve anti-tumor effects. The anti-tumor effect was achieved. In another study, metformin was also observed to inhibit the proliferation of MMQ cells and similar mitochondria-mediated apoptosis and experimental results were observed. Also in another study, it was observed that metformin inhibited the proliferation of ACTH-secreting mouse pituitary cortical dystrophoma cells A1T20, promoted apoptosis and reduced ACTH secretion, but did not prevent the cell cycle. Metformin-induced apoptosis was accompanied by an increase in caspase-3 activity, while metformin downregulated the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2) but upregulated the pro-apoptotic protein BAX, suggesting the involvement of a mitochondria-mediated apoptotic pathway. However, it has also been suggested that metformin was not observed to increase apoptosis in GH3 pituitary tumor cells, and whether this may be due to the experimental design as well as the nutritional environment needs to be further verified.

2.2 AMPK-mediated related pathways

In the study, AMPK was found to mediate growth inhibition or apoptosis of many types of tumor cells. While metformin, an activator of AMPK pathway It has been suggested that it activates AMPK by restricting complex I in the mitochondrial respiratory chain, generating cellular energy stress, and thus activating AMPK and indirectly by increasing the [AMP]/[ADP] ratio. It is not clear what its role is in pituitary tumors, raising concerns about its mechanism of action in pituitary tumor cells.

Previous work has noted sex-dependent effects of MET on serum PRL levels, suggesting that the hypothalamic-pituitary-gonadal axis may be a target of metformin, and one study has investigated the AMPK agonist by measuring AMPK
phosphorylation in human primary prolactinoma samples and using BC-sensitive MMQ cells and BC-resistant GH3 cells and their xenografts as models. The role of MET in prolactinoma and the downstream effectors were investigated. It is proposed that AMPK signaling is inhibited in D2R-positive BC-resistant human prolactinomas. The AMPK activator MET inhibited the proliferation of BC-sensitive (MMQ) and drug-resistant (GH3) prolactinoma cells. It has been shown that bromocriptine resistance is associated with downregulation of AMPK activity and high estrogen receptor expression, and that MET downregulates ERα and ERβ by activating the AMPK signaling pathway and inhibits prolactinoma growth and PRL secretion.[34] MET inhibits prolactinoma growth and PRL secretion by activating the AMPK signaling pathway.

It has been shown that metformin enhances p-AMPK expression and decreases p-mTOR expression in MMQ cells, and Compound C, an AMPK inhibitor, reduces the inhibitory effect of metformin on p-mTOR expression. It is suggested that metformin activates the AMPK/mTOR pathway, which may be part of the mechanism to inhibit MMQ cell proliferation, induce apoptosis and G0/G1 phase block.[23] Meanwhile, metformin significantly increased the levels of phosphorylated AMPK, phosphorylated AKT and phosphorylated mTOR in AtT20 cells in a dose-dependent manner, representing that metformin activated AMPK and inhibited mTOR in AtT20 cells, suggesting that the activation of AMPK/mTOR signaling pathway may be related to metformin-induced proliferation inhibition and apoptosis promotion in AtT20 cells. However, it remains to be verified whether the activation of AMPK is related to the reduction of hormone secretion.[26].

Whereas in another study it was found that on GH-secreting PitNET cells, metformin induced GH3 cells to inhibit the target of EGF-induced mTOR-p70S6 6 kinase signaling pathway was suggested as a potential mechanism, downstream possible EGF receptors were incorporated into AMPK substrates indicating that membrane receptors are direct targets and may be involved in mediating their inhibitory effects on cell growth, in this study In the present study, we limited ourselves to demonstrating the presence of
AMPK targets including cell surface receptors in GH3 cell membrane protein fractions\[27].
Calcium has been reported to be a relevant second messenger for pituitary cell physiology. It has been shown that the effect of metformin on PitNET may involve AMP-activated protein kinase-dependent Calcium kinetics altering cell viability, but the altered Calcium kinetics induced in different pituitary tumor cells are different, suggesting that metformin inhibits different types of pituitary tumor cells differently, and that the altered calcium kinetics found appear to be related to hormone secretion [33].

2.3 ATF-3-mediated pathway
ATF3 is a stress response transcription factor belonging to the ATF/CREB family. In the present study, ATF3 was found to be upregulated by metformin, and its knockdown significantly reduced metformin-induced apoptosis, suggesting that ATF-3 may mediate the pro-apoptotic effect of metformin. The inhibitory effect of compound C on AMPK did not alter the inhibitory effect of metformin on STAT3 activity, suggesting that metformin may reduce GH secretion by inhibiting non-AMPK-dependent STAT3 activity. Metformin also significantly inhibited cell proliferation and GH secretion in primary human GH-PA cells. Upregulation of ATF3 and downregulation of p-STAT3 were also demonstrated in xenografts. It was revealed that metformin inhibited the growth of somatic dystrophic adenoma cells both in vitro and in vivo through ATF-3-mediated pro-apoptotic effects. These findings suggest that metformin is a potentially promising therapeutic agent for the treatment of GH-PA.\[24] The findings suggest that metformin is a potential promising therapeutic agent for the treatment of GH-PA.

2.4 IGF-1R-mediated pathway
IGF-1R is an important growth factor receptor that activates the downstream phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway upon binding to IGF-1, and its overactivation is associated with tumor development. The IGF-1R, p-AKT (S473), and p-ERK levels decreased with increasing metformin concentration after metformin treatment. The IGF-1R inhibitor PPP inhibited MMQ cell proliferation, suggesting that
metformin may inhibit cell proliferation by inhibiting the IGF-1R pathway in MMQ cells.[25] The results suggest that metformin may inhibit cell proliferation by inhibiting the IGF-1R pathway in MMQ cells. In another study, metformin decreased IGF-1R expression, AKT (S473) phosphorylation and mTOR (Ser2448) phosphorylation, which inhibited AtT20 cell proliferation, while PPP (IGF-1R inhibitor) significantly inhibited AtT20 cell proliferation in a dose-dependent manner, suggesting that IGF-1R plays a tumor progression role in pituitary corticotropin important role. In view of the above, we suggest that metformin may inhibit AtT20 cell proliferation by suppressing the IGF-1R/AKT/mTOR signaling pathway[26].

3. Discussion

It is known from the above studies that there may be multiple pathways for the effect of metformin on pituitary tumors, but the complete mechanisms of the different pathways are not all clear as well as the findings and opinions on the same pathway are not entirely consistent, and with some bias excluded, it has been suggested that it may be due to the effect of metformin acting on different cells as well as different environments, and it has been pointed out that the effect of metformin at the cellular level depends on the metabolic characteristics and metabolic demands of the cells, and the tumor microenvironment may influence this response, however pyruvate metabolism branching points are most likely to play a major role in the variability of the cellular response to metformin, a role supported by significant differences in PDH complex expression levels between myogenic cells and pituitary tumor cells[26]. The above research conducted in vitro and relevant research data and clinical trials are still limited or unavailable, so more evidence is needed to verify the accuracy of the individual ideas.

There is research evidence that it is not feasible to achieve high concentrations of metformin in in vitro experiments in humans[27,28] The observation that the prevalence of various tumor types is lower in patients with type 2 diabetes on regular metformin doses and that serum concentrations of metformin are much lower than those that
inhibit cancer cells *in vitro* raises the possibility that the mechanism of tumor prevention *in vivo* with regular therapeutic doses of metformin may be largely indirect and related to metformin ameliorating such metabolic or hormonal abnormalities such as obesity, hyperglycemia and hypertension. It is also important to consider that there may be physiological metabolic differences between rat pituitary tumor cell lines and human pituitary tumor cell lines, among others.

Despite these studies, metformin has not really been used as a clinical treatment for pituitary tumors. There have been case reports of reduced prolactin levels and tumor size in two patients treated with a combination of bromocriptine and metformin, whereas bromocriptine alone was not sufficient to reduce prolactin levels or slow tumor growth. In another case report, the combination of bromocriptine and metformin reduced prolactin levels and tumor size. In another case report, the combination of metformin and capsaicin did not show consistent inhibition of serum prolactin levels in either the short or long term in 10 patients with lactinoma resistant to capsaicin. Additional studies have evaluated the effects of metformin on cell viability and hormone secretion when combined with other agents, for example, metformin/SSA combination therapy did not increase the effectiveness of SSA monotherapy, but appeared to increase the role of octreotide in GHomas. For example, metformin/SSA combination did not increase the effectiveness of SSA monotherapy but appeared to increase the role of octreotide in GHomas, and MET + BC significantly inhibited PRL secretion, further reducing tumor growth and serum PRL levels in xenografts compared to BC treatment alone. However, in the face of metformin treatment, the tumor growth and serum PRL levels in xenografts were further reduced. However, in the face of ineffective metformin treatment, the possibility that metformin responds to patients cannot be dismissed. The heterogeneity among patients with pituitary tumors and the diversity of drug treatment options add to the complexity of disease treatment, and further studies are needed to demonstrate whether treatment with metformin alters the risk of pituitary tumor morbidity and mortality, such as determining the dose and duration of treatment and the effect when combined with other drugs, and whether it is
reasonable to use metformin to treat pituitary tumors in patients without diabetes and the side effects or complications of using different concentrations of metformin in humans, which could help to improve the management of pituitary tumor patients in a more individualized manner. Given the available data, the use of metformin medication may be a promising and clinically relevant option for patients with pituitary tumors, and further studies are needed to confirm its clinical relevance as an adjuvant or new therapy and to further develop a comprehensive understanding of the potential antitumor mechanisms of metformin in pituitary tumors to determine the true efficacy of metformin in the treatment of pituitary tumors.

CONCLUSION

Metformin, a traditional hypoglycemic drug, has been newly discovered to have multiple functions, including antitumor effects. There have been studies on the mechanism of metformin for the treatment of pituitary tumors, but it is of great significance whether it will provide new adjuvant or alternative therapies for the treatment of pituitary tumors.
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