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Original Article

Effects of tetrandrine and caffeine on cell viability and expression of mammalian target of rapamycin, phosphatase and tensin homolog, histone deacetylase 1, and histone acetyltransferase in glioma cells

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ABSTRACT

Objective: Knowledge about the mechanisms underlying the cytotoxicity of tetrandrine and caffeine on glioma cells is limited. The primary objective of this study was to assess the expression of mammalian target of rapamycin (mTOR), phosphatase and tensin homolog (PTEN), histone deacetylase 1 (HDAC1), and histone acetyltransferase (p300) in RT-2 glioma cells treated with caffeine and/or tetrandrine.
Materials and methods: The cell viability and expression of mTOR, PTEN, HDAC1, and p300 in RT-2 glioma cells were assayed after treatment with caffeine and/or tetrandrine for 48 hours.
Results: The cell viability of RT-2 cells decreased significantly 48 hours after treatment with tetrandrine (5 μM) alone and tetrandrine (5 μM) combined with caffeine (0.5 mM or 1 mM), but not caffeine (0.5 mM or 1 mM) alone. The protein levels of mTOR, PTEN, and HDAC1 did not appear to change significantly after treatment with caffeine (0.5 mM or 1 mM) alone, tetrandrine (5 μM) alone, or their combinations. However, p300 increased significantly after treatment with caffeine (0.5 mM or 1 mM) alone, tetrandrine (5 μM) alone, and their combinations.
Conclusion: Tetrandrine and caffeine can increase glioma cell death additively possibly via increasing p300 expression.

1. Introduction

Malignant glioma is the most common primary brain tumor in adults. The prognosis of patients with glioblastoma remains very poor [1], and development of new drugs is urgently needed. The poor prognosis of malignant glioma is largely attributable to a highly deregulated tumor genome with opportunistic deletion of tumor suppressor genes, amplification and/or mutational hyperactivation of receptor tyrosine kinase receptors, and defects in the apoptosis signaling machinery [2].

A previous study showed that phosphatidylinositol 3 kinase (PI3K)/protein kinase B (Akt) is overexpressed in glioma cells [3]. Mammalian target of rapamycin (mTOR) is a PI3K-related serine/threonine kinase and can regulate cell proliferation, growth, differentiation, and survival [4]. Phosphatase and tensin homolog (PTEN), as a tumor suppressor gene, can downregulate the PI3K-mediated cell signaling pathway via acting on Akt. However, PTEN is often inactivated in many cancer cells, including melanoma, glioma, and cancers of the breast, prostate, and endometrium [5,6].

Histone deacetylases (HDACs) and histone acetyl transferases (HATs) are involved in determining the state of acetylation of histones and are early steps in genetic transcription [7]. There are reports that altered activities of HDACs and HATs are associated with cancer formation. For example, overexpression of HDAC1 has been associated with human gastric and prostate cancers, and malignant glioma [8]. Thus, HDAC1 has recently become recognized

Conflict of interest: none.

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as a promising target for cancer therapy, including treatment of malignant glioma. The decreased expressions of HATs have also been associated with several diseases, such as cardiac hypertrophy, asthma, and cancers [9]. Loss of heterozygosity of HAT p300 was found in 80% of malignant glioma [10].

Previous studies showed that caffeine and tetrandrine have antiglioma effects [11–16]. Caffeine can attenuate the G2 delay produced by cisplatin and camptothecin, and enhance the cytotoxicity of cisplatin and camptothecin in human brain tumor cell lines [16]. Caffeine has been reported to inhibit some kinase activities, including various forms of mTOR and PI3K, in tumor cells [17]. Moreover, caffeine can increase PTEN expression, leading to PI3K–AKT pathway inactivation, and block osteosarcoma cell proliferation [18]. However, the effects of caffeine on the expression of HDAC1 and p300 in glioma cells are still unknown. Tetrandrine is a bis-benzylisoquinoline alkaloid and can increase P38 and mitogen-activated protein kinase activity, exert antiangiogenesis, and induce the caspase-dependent cell death pathway [11–13]. However, the effects of tetrandrine on the expression of mTOR, PTEN, HDAC1, and p300 in glioma cells are still unknown.

In this experimental study, we aimed to investigate the effects of caffeine and tetrandrine on cell viability and expression of mTOR, PTEN, HDAC1, and p300 in malignant glioma cells. We hypothesized that caffeine and tetrandrine could increase the cell death of RT2 glioma cells additively via decreasing mTOR and HDAC1 expression, and increasing PTEN and p300 expression.

2. Materials and methods

2.1. Cell line

RT-2 cells were derived from an avian sarcoma virus-induced brain tumor in the Fischer 344 rat. This cell line was provided by the National Taiwan University Hospital, Taipei, Taiwan [12,13], and maintained in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum, 2 mM L-glutamate, and 100 U/mL penicillin at 37°C in a humidified incubator with a 5% CO_2 atmosphere.

2.2. Cell viability assay

Cell viability was measured at 48 hours after treatment with various concentrations of caffeine (0 mM, 0.5 mM, 1 mM, 2 mM, and 5mM) and/or tetrandrine (0 μM, 5 μM, 10 μM, and 15 μM) using a colorimetric assay for 96-well plates with 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2*H*-tetrazolium monosodium salt (WST-1) reagent. Each plate contained blanks, controls, and treatment groups. Treatment consisted of addition of 10 μL of Premixed WST-1 Cell Proliferation Reagent (Abcam, USA) to each well (1:10 final dilution).

The plate was incubated for 4 hours at 37°C in a humidified atmosphere maintained at 5% CO_2. The absorbance was measured at 450 nm (reference wavelength, 690 nm) using a multiwell plate reader.

2.3. Western blot analysis

Low concentrations of caffeine (0 mM, 0.5 mM, and 1 mM) and/or tetrandrine (0 μM and 5 μM) were chosen for Western blot analysis at 48 hours after the cell viability assay. Both adherent and floating cells were collected. The cell pellets were resuspended with radioimmunoprecipitation assay lysis buffer and lysed at 4°C for 30 minutes. After 65,000 g centrifugation for 30 minutes, the protein content of the supernatant was determined using the bicinchoninic acid protein assay. Equal amounts of the total protein were separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to nitrocellulose membranes, which were soaked in blocking buffer (1% bovine serum albumin). Proteins were detected using polyclonal antibodies against mTOR and PTEN, and then visualized using goat-antirabbit immunoglobulin G conjugated with horseradish peroxidase as the horseradish peroxidase substrate. The expression levels of mTOR and PTEN were presented as relative ratios in comparison to β-actin.

2.4. HDAC1 activity assay

Assays were performed using the enzyme-linked immunosorbent assay (ELISA) Assay Kit for HDAC1from USCN Life Sciences (Wuhan, Hubei, China) according to the manufacturer's instructions. Briefly, 100 μL of cells, standard, and blank were added to each well, and incubated for 2 hours at 37°C. Next, the liquid from each well was removed. Detection Reagent A (100 μL) was added, and the plate was incubated for 1 hour at 37°C. This was followed by aspiration, and the solution was washed three times. The wells were added with Detection Reagent B (100 μL), then incubated for 30 minutes at 37°C. Aspiration followed, and the solution was washed five times. Next, 90 μL Substrate Solution was added, followed by incubation for 20 minutes at 37°C. Then, Stop Solution (50 μL) was added and ELISA plate reader at 450 nm. HDAC1 activity was expressed as the relative optical density values per nanogram of the protein sample.

2.5. HAT (p300) activity assay

Assays were performed using the HAT activity colorimetric assay from BioVision (BioVision Research Products, Mountain View, CA, USA) according to the manufacturer's instructions. Briefly, 50 μg of purified proteins from cells were diluted in 40 μL of ddH_2O; 68 μL of Assay Mix was then added, followed by incubation at 37°C for 1–4 hours. Samples were then read in an ELISA plate reader at 440 nm. HAT (p300) activity was expressed as the relative optical density values per microgram of the protein sample.

2.6. Statistical analysis

The data are presented as the mean ± standard deviation, unless indicated otherwise. The expression levels of mTOR, PTEN, HDAC1, and p300 were compared separately between all groups by one-way analysis of variance (ANOVA) with *post-hoc* Bonferroni correction. All analyses were performed using the commercialized software STATA10, and $p < 0.05$ was considered statistically significant.

Data are representative of three independent experiments (error bars, standard deviation of triplicate samples).

3. Results

Fig. 1 shows the effects of various concentrations of caffeine (0 mM, 0.5 mM, and 1 mM) and/or tetrandrine (0 μM and 5 μM) on the cell viability of RT2 glioma cells at 48 hours. Compared with the control group without caffeine or tetrandrine treatment, the cell viability decreased significantly when RT-2 cells were treated with tetrandrine in various concentrations (5 μM) alone, and combined with caffeine (0.5 mM or 1 mM; one-way ANOVA, $p < 0.0001$; *post-hoc* Bonferroni correction, $p < 0.001$ for each concentration). Compared with tetrandrine treatment (5 μM) alone, the cell viability decreased significantly when RT-2 cells were treated with combined tetrandrine (5 μM) and caffeine (1 mM; one-way ANOVA, $p < 0.0001$; *post-hoc* Bonferroni correction, $p < 0.001$ for each concentration).

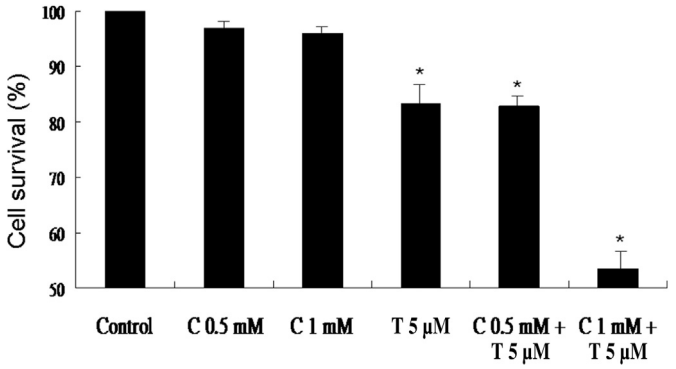

Fig. 1. Effects of various concentrations of caffeine (0 mM, 0.5 mM, and 1 mM) and/or tetrandrine (0 μM and 5 μM) on the cell viability of RT2 glioma cells at 48 hours. Cell viability decreased significantly when RT2 cells were treated with tetrandrine (5 μM) alone, or combinations of tetrandrine (5 μM) and caffeine (0.5 mM or 1 mM).

Fig. 2 shows the ratio of mTOR versus β-actin expression with various concentrations of caffeine (0.5 mM or 1 mM) and/or tetrandrine (5 μM) in RT-2 glioma cells. The expression of mTOR was not significantly different in any treatment group (one-way ANOVA, $p = 0.8981$), although mTOR expression tended to decrease under treatment with caffeine (0.5 mM or 1 mM) and/or tetrandrine (5 μM).

Fig. 3 shows the ratio of PTEN versus β-actin expression with various concentrations of caffeine (0.5 mM or 1 mM) and/or tetrandrine (5 μM) in RT-2 glioma cells. The expression of PTEN was not significantly different in any treatment group (one-way ANOVA, $p = 0.6961$), although PTEN expression tended to increase under treatment with caffeine (0.5 mM or 1 mM) and/or tetrandrine (5 μM).

Fig. 4 shows the concentration of HDAC1 with various concentrations of caffeine (0.5 mM or 1 mM) and/or tetrandrine (5 μM) in RT-2 glioma cells. The expression of HDAC1 was not significantly different in any treatment group (one-way ANOVA, $p = 0.1445$), although HDAC1 expression tended to decrease under treatment with caffeine (0.5 mM or 1 mM) and/or tetrandrine (5 μM).

Fig. 5 shows the concentration of p300 with various concentrations of caffeine (0.5 mM or 1 mM) and/or tetrandrine (5 μM) in RT-2 glioma cells. The expression of p300 was significantly different

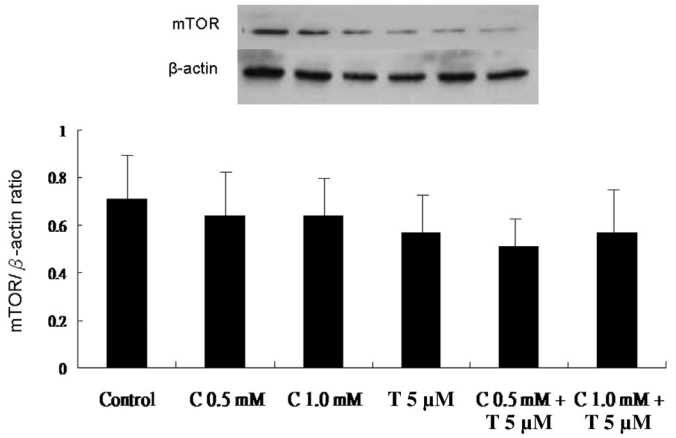

Fig. 2. Ratio of mammalian target of rapamycin (mTOR) versus β-actin expression with various concentrations of caffeine (0.5 mM or 1 mM) and/or tetrandrine (5 μM) in RT-2 glioma cells. Expression of mTOR was not significantly different in any treatment group (one-way analysis of variance, $p = 0.8981$), although mTOR expression tended to decrease after treatment with caffeine (0.5 mM or 1 mM) and/or tetrandrine (5 μM).

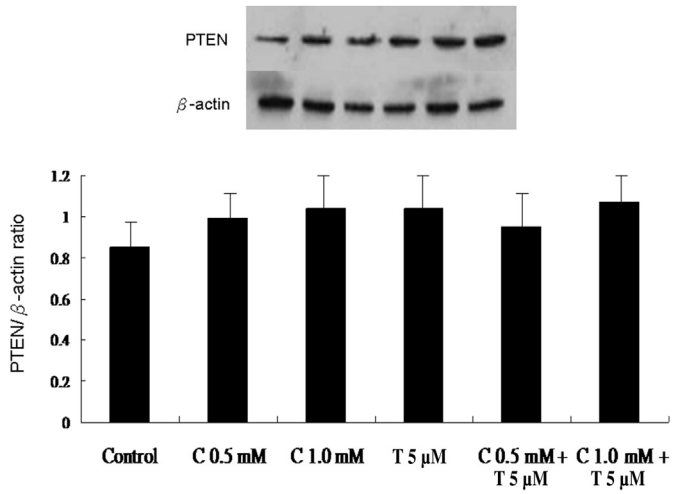

Fig. 3. Ratio of phosphatase and tensin homolog (PTEN) versus β-actin expression with various concentrations of caffeine (0.5 mM or 1 mM) and/or tetrandrine (5 μM) in RT-2 glioma cells. Expression of PTEN was not significantly different in any treatment group (one-way analysis of variance, $p = 0.6961$), although PTEN expression tended to increase after treatment with caffeine (0.5 mM or 1 mM) and/or tetrandrine (5 μM).

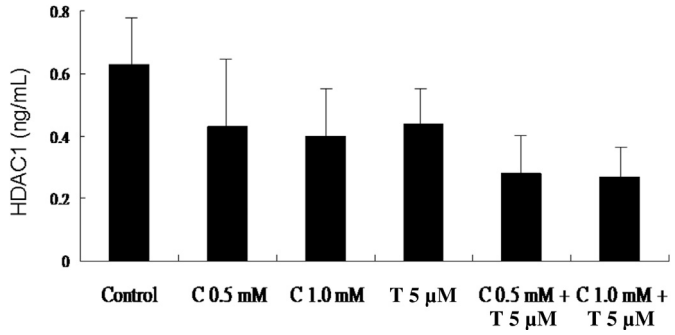

Fig. 4. Concentration of histone deacetylase 1 (HDAC1) with various concentrations of caffeine (0.5 mM or 1 mM) and/or tetrandrine (5 μM) in RT-2 glioma cells. Expression of HDAC1 was not significantly different in any treatment group (one-way analysis of variance, $p = 0.1445$), although HDAC1 expression tended to decrease after treatment with caffeine (0.5 mM or 1 mM) and/or tetrandrine (5 μM).

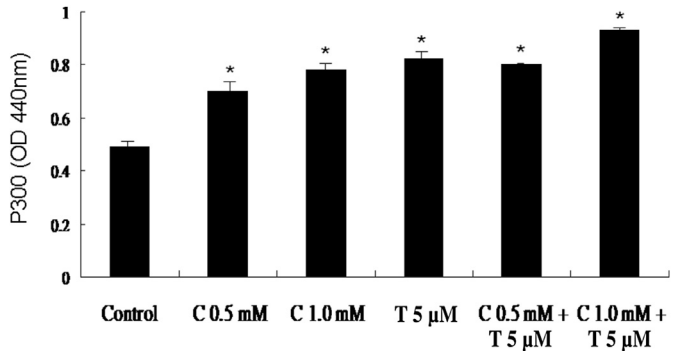

Fig. 5. Concentration of p300 with various concentrations of caffeine (0.5 mM or 1 mM) and/or tetrandrine (5 μM) in RT-2 glioma cells. Expression of p300 was significantly different in all treatment groups (one-way analysis of variance, $p < 0.0001$). Compared with the control group (0.486 ± 0.016), p300 expression increased significantly with caffeine (0.5 mM or 1 mM) alone (0.702 ± 0.038, $p < 0.001$; 0.782 ± 0.040, $p < 0.001$), tetrandrine (5 μM) alone (0.815 ± 0.046, $p < 0.001$), and combined treatment with tetrandrine (5 μM) and caffeine (0.5 mM or 1 mM) (0.804 ± 0.010, $p < 0.001$; 0.932 ± 0.015, $p < 0.001$).

in all treatment groups (one-way ANOVA, $p < 0.0001$) compared with the control group. Relative to the control group (0.486 ± 0.016), the p300 expression increased significantly with caffeine (0.5 mM or 1 mM) alone (0.702 ± 0.038, $p < 0.001$; 0.782 ± 0.040, $p < 0.001$), tetrandrine (5 μM) alone (0.815 ± 0.046, $p < 0.001$), and combined treatment with tetrandrine (5 μM) and caffeine (0.5 mM or 1 mM; 0.804 ± 0.010, $p < 0.001$; 0.932 ± 0.015, $p < 0.001$).

4. Discussion

This experimental study showed that caffeine and tetrandrine can increase glioma cell death additively via increasing p300 expression. However, the expression of mTOR, PTEN, or HDAC1 did not change significantly after treatment with caffeine or tetrandrine alone or in combination. Previous studies showed that the PI3K/Akt/mTOR signaling pathway is overexpressed in glioma cells. On the contrary, blockade of PI3K/Akt/mTOR signaling could induce caspase-dependent apoptosis and increase autophagy in glioma cells [3,4]. PTEN is a negative regulatory protein of the mTOR and PI3K signaling pathway, but is often inactivated in glioma [5,6]. PTEN mutations can result in activated PI3K/Akt survival signaling associated with resistance to radiotherapy [19]. HDAC1 is a predominantly nuclear protein with ubiquitous expression. The expression of HDAC1 is induced upon growth factor activation, and increased in highly proliferative tissues, embryonic stem cells, several transformed cell lines, and in the majority of cancers [20,21]. HAT is also essential for the physiological processes of cell proliferation, differentiation, and apoptosis [22]. The decreased expression or mutations of HATs have been associated with several diseases, such as cardiac hypertrophy, asthma, and several types of cancer [9,10].

Caffeine has been reported to inhibit some kinase activities, including various forms of mTOR and PI3K, in tumor cells [17]. Caffeine also reduces glioma cell proliferation through G(0)/G(1)-phase cell cycle arrest by suppressing retinoblastoma protein phosphorylation [23]. Furthermore, caffeine can increase PTEN expression, leading to PI3K–AKT pathway inactivation, and block osteosarcoma cell proliferation [18]. Caffeine confers radiosensitization of PTEN-deficient malignant glioma cells by enhancing ionizing radiation-induced G1 arrest and negatively regulating Akt phosphorylation [19]. Caffeine can induce apoptosis through both the caspase-dependent (caspase-3) and -independent [poly(ADP-ribose) polymerase cleavage] cell apoptosis signaling pathways [11–13]. In this study, however, caffeine did not decrease mTOR expression or increase PTEN expression significantly as reported in previous studies [17,18]. This discrepancy might have been due to differences in cell lines and/or caffeine concentrations. However, we provided a novel finding that caffeine alone or combined with tetrandrine tended to decrease HDAC1 expression and increased p300 expression significantly in RT2 cells.

Tetrandrine can produce free radical damages, stop progression of the cell cycle, increase mitogen-activated protein kinase activity, reverse multidrug resistance, exert antiangiogenesis, and induce caspase-dependent apoptosis in various cancer cells, including glioma and/or neuroblastoma cells [11–13,24]. Tetrandrine also exerts radiosensitization in glioma cells by elimination of radiation-induced cell cycle perturbation [11–13]. In this study, we showed that tetrandrine alone or in combination with caffeine can increase p300 expression significantly in RT2 cells, although the expression of mTOR, PTEN, and HDAC1 was not significantly altered.

Histone acetylation has been shown to induce transcriptional activation. A previous study showed that ethanol could increase acetylation of H3 at Lysine 9 through modulation of HAT, and this acetylation can be regulated by the extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) signaling pathways [25]. Mitogen-activated protein kinases (MAPK; ERK1/2, p38 MAPK, and JNK) can also phosphorylate several types of HATs (e.g., CREB-binding protein, activating transcription factor 2, and steroid receptor coactivator 1) and directly increase their enzymatic activities [25,26], or indirectly regulate HAT activity by modifying the signaling pathways affecting HAT activity [27,28]. We also found that caffeine and tetrandrine could increase p300 levels, which is helpful for cancer treatment.

5. Conclusion

Combined treatment with caffeine and tetrandrine could increase glioma cell death additively possibly via increasing p300 expression. This combination might be a candidate for human glioma chemotherapy in the future.

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