



Research Article

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Single Versus Double Ring Structure: Search for Best Anti-Neoplastic Driver in Colon and Pancreatic Cancer Cells -Taurultam or Taurolidine?

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Abstract

Background: Since the molecular mechanism of the well-known anti-infective and antineoplastic substance Taurolidine (TRD) is still unknown, we sought to analyze the antineoplastic capacity of its main metabolite Taurultam (TAU) in malignant human cell lines derived from pancreatic cancer (AsPC-1, BxPC-3, HPAF II, MiaPaca-2, Panc-1) and colon cancer (SW-480, HT-29 and HCT-116) *in vitro*.

Methods: Cell lines were incubated with TAU or TRD in increasing concentrations for 24 h and 48 h. Comprehensive analyses were performed to quantify the antineoplastic activity of TAU: Analysis of cytotoxicity via MTT-assay, inhibition of proliferation via BrdU and induction of apoptosis and necrosis via FACS-analysis. Furthermore, cell growth was monitored using a real-time cell analyzer.

Results: TAU revealed a significant cytotoxic and anti-proliferative effect on all pancreatic and colon cancer cell-lines as well in MTT- and BrdU- assays as in the real-time cell analyzer. Furthermore, FACS analyses were characterized by a significant apoptotic and necrotic response upon stimulation with TAU. In contrast to TRD antineoplastic effects were noticeable lower.

Conclusion: It could be demonstrated for the first time, that TAU provides antineoplastic effects operating through mechanisms like its parent compound TRD. However, our results show clearly that TAU is not the only antineoplastic active metabolite of TRD. Hence, our data suggest that the efficiency of TRD against cancer cells is rather based on the methylol-containing species released during hydrolysis. These promising results are the first step towards the development of a novel substance combining the high antineoplastic capacity of TRD with better molecular properties of TAU, like a higher solubility in aqueous solution.

Keywords

MTaurolidine; Taurultam; Apoptosis; Chemotherapy; Cancer; Methylol-containing species; Gastrointestinal cancer

Abbreviations: Annexin V-FITC: Annexin V-Fluorescein; BrdU: 5-bromo-2-deoxyuridine; CI: Cell index; DMEM: Dulbecco's modified eagle medium; DMSO: Dimethylsulfoxide; ELISA: Enzyme

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Linked Immunosorbent Assay; FACS: Fluorescence-activated cell scanning; NAC: N-acetylcysteine; PCD: Programmed cell death; PDAC: Pancreatic ductal adenocarcinoma; PI: Propidiumiodide; RPMI 1640: Roswell park memorial institute medium 1640; TRD: Taurolidine; TAU: Taurultam; Z-VAD: carbobenzoxy-valyl-alanyl-aspartyl-[O-methyl]-fluoromethylketone

Introduction

Taurultam is a metabolite of Taurolidine (bis (1,1-dioxoperhydro -1,2,4 - thiadiazinyl - 4) methane) and consists of one annular structure [1]. Two molecules of Taurultam rise by hydrolysis of Taurolidine (double ring structure) and are metabolized first to tauramide and further to Taurine and CO₂ [2]. Originally taurolidine is an antimicrobial substance, which is successfully used in the treatment of bacterial and fungal induced infections, like peritonitis [4,5]. Furthermore Taurolidine is used for the successful treatment and prophylaxis of catheter associated infections [6,7]. This antimicrobial effect has caused by Methylol-containing species, which are created during the hydrolysis of Taurolidine (Figure 1) and interact with bacterial and fungal cell walls [8,9].

In 1997 the antineoplastic effect of Taurolidine was first demonstrated by Jacobi et al., *in vitro* in colon carcinoma cells and *in vivo* in a rat model [10]. Additional investigations confirmed this effect in different malignant cells *in vitro* [11-16] as well as *in vivo* [14,16-19]. The mechanisms of its anti-neoplastic activity are not completely understood yet, but it is known that in an aqueous solution a chemical equilibrium between Taurolidine and (one of) its metabolite Taurultam exists, where the equilibrium is strongly shifted in the direction of the metabolite and Taurolidine is presented in a low concentration (2-10%) [2]. Therefore, the aim of this investigation was to examine the anti-neoplastic effect of Taurultam the major breakdown product separately for the first time, to find out whether the anti-neoplastic activity of Taurolidine mainly relies on the effects of this metabolite. The antineoplastic effect of the single ring structured Taurultam was never evaluated using human cancer cell lines before. Therefore this study focuses on the anti-proliferative capacity, the induction of cell death and the dose depending formation of apoptosis and necrosis by Taurultam using different established human cancer cell lines from colon carcinoma and pancreatic cancer. These model cell lines were tested for the effects of Taurolidine and showed the desired response in former investigations [20,21].

Material and Methods

Cell culture and cell lines

Six different cancer cell lines: AsPC-1, CLS Cell Lines Service, Eppelheim, Germany, BxPC-3 ATCC - LGC Standards GmbH, Wesel, Germany, HPAF II, HCT116, SW480, HT 29 American Type Culture Collection, and Manassas were used in this study. HPAF II cells were cultured in Eagles' Minimum Essential Medium (MEM Eagle) (PAN Biotech GmbH, Aidenbach, Deutschland). AsPC-1 cells and BxPC-3 cells were cultured in RPMI 1640 (PAN Biotech GmbH, Aidenbach), the remaining cell lines (HCT116, HT29 and SW480) were cultured in Dulbecco's Modified Eagle Medium (PAN Biotech GmbH, Aidenbach, Germany). Cell cultures were supplemented

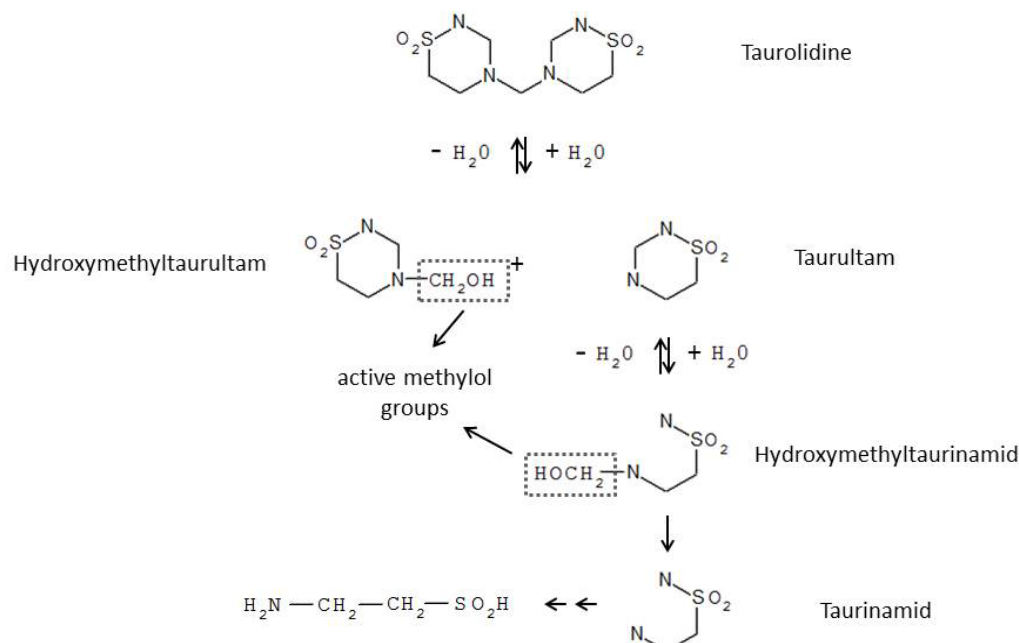


Figure 1: The formation of the metabolites of Taurolidine. In an aqueous solution Taurolidine exists in a chemical equilibrium with Taurultam and Hydroxymethyl-Taurultam. Taurultam metabolizes to Hydroxymethyl- Taurinamid and further to Taurine.

with 10% fetal bovine serum (Biowest Ltd., Nuaillé, Frankreich), 1% Penicillin (10000 U/ml) and Streptomycin (10000 U/ml) (Biowest Ltd., Nuaillé, Frankreich) as well as 1% L-Glutamin (Biowest Ltd., Nuaillé, Frankreich). The cells were cultured at 5 % (v/v) CO_2 , 37.0°C and 95% humidity.

Reagents

Taurolidine (TRD) and Taurultam (TAU) were synthesized, collected and given by Doctor RW Pfirrmann and therefore kindly provided by Geistlich Pharma (Wohlhusen, Switzerland). Taurultam were dissolved in double distilled water; Taurolidine was dissolved in a 5% Povidon (Geistlich Pharma AG, Wolhusen, Switzerland). To be able to compare both substances accurately Tau was always used in a doubled concentration, because 1 Mol TRD is hydrolyzed within the human body into 2 Mol of TAU.

Viability assay MTT

Cytotoxic effects were measured by colorimetric MTT assay (Sigma-Aldrich, Steinheim, Germany). Cells (45000/well) were seeded in a 96-well-format. After 24 hours, cells were treated with different concentrations of TAU for 24 h and 48 h. In order to determine a dose-response effect of TAU, various concentrations of TAU (100 μM , 200 μM , 500 μM , 1000 μM , 1500 μM and 2000 μM) were used. Two concentrations of TRD (250 μM and 1000 μM) served as positive controls, whereas the solvent of the respective substances (5% Povidon solution and double-distilled water) were used as negative controls.

BrdU proliferation assay

Anti-proliferative effect was measured by BrdU (5-bromo-2'-deoxyuridine) incorporation (Cell Proliferation ELISA, BrdU colorimetric, Roche Applied Science, Mannheim, Germany). Cells (45000/well) were seeded in a 96-well-plate. After 24 h the medium was removed and the cells were incubated with scheduled concentrations of TAU (100 μM , 200 μM , 500 μM , 1000 μM , 1500 μM and 2000

μM). After an incubation period of 6 h the BrdU reagent was added and left for additional 2 h, before cells were introduced to the BrdU proliferation assay (Roche), following the manufactures instructions. Positive and negative controls were used according to the MTT assay. The incubation period add up to 8 h, which showed to be an adequate incubation time in previous investigations [22].

Flow cytometry analysis

Two pancreas carcinoma (AsPc-1, BxPC-3) and two colon carcinoma cell lines (HCT116 and SW480) were incubated with various concentrations of TAU (200 μM , 500 μM and 2000 μM) and TRD (250 μM and 1000 μM) and analyzed by flow cytometry. A 5% povidone solution and double distilled water served as controls. After 24h all cells were collected and resuspended in binding buffer (rh-annexin V -FITC kit, Bender Med Systems GmbH, Vienna, Austria). Dilutions of 200 cells/ μl were stained using Annexin V-FITC (BD Biosciences, Heidelberg, Germany) and Propidiumiodid (BenderMed Systems GmbH, Vienna, Austria). Dot plots were analyzed using Cell Quest Pro software. Annexin V-FITC negative and PI negative cells were considered viable. Annexin V-FITC positive however PI negative cells were assumed as apoptotic. Annexin V-FITC negative and PI positive cells were labeled necrotic.

xCELLigence system

Cells (6000/well) were seeded in a 16-well-e-plate format and incubated at 37°C with 5% CO_2 for 24 h before treated with scheduled concentrations of TAU (200 μM , 500 μM , 2000 μM) or TRD (100 μM , 1000 μM). Cells were monitored by the xCELLigence system every 10 minutes for up to 48 h. Double distilled water and 5% povidone solution served as controls.

Statistical analysis

Depending on the cell line and the assay, four to six passages were incubated with TAU or TRD. Results of the viability Assay MTT,

the proliferation assay BrdU and the flow cytometric analysis were statistically evaluated using the data processing program Graphpad Prism software. The results were expressed as mean value and its standard deviation (mean \pm SEM).

For comparison one way ANOVA with Tukey's post-hoc test was performed. P-values ≤ 0.05 were regarded as statistically significant: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$, n.s.= not significant.

Results

Taurultam and Taurolidine introduce cell death in different cancer cell lines

To evaluate the cytotoxic effect of TAU compared to TRD MTT assays were used. The results of the viability assay after treatment with several concentrations of TAU and TRD over 24h and 48h showed a statistically significant decrease of cell viability in all cell lines. After 24h (Figure 2) a response was noticed starting with a concentration of 200 μ M TAU in three cell lines (HPAF II, HT-29 and SW480). Values of cell viability rates were measured between $90.1 \pm 1.9\%$ (SW480) and $87.9 \pm 0.9\%$ (HT-29). In the presence of 1000 μ M TAU all cell lines showed a reduction of cell viability, reaching values from $68.9 \pm 2.1\%$ (HPAF II) up to $30.9 \pm 4.9\%$ (BxPC-3). Cells incubated with 1500 μ M and 2000 μ M showed also massive cell death. Similar results appeared after 48h (data not shown). The strongest decrease of cell viability was observed from 1000 μ M up to 2000 μ M, leading to cell viability rates between $50.0 \pm 2.8\%$ (HPAF II) and $13.7 \pm 5.1\%$ (BxPC-3). However, TRD tends to be more effective in the reduction of viable cells, where both concentrations of TRD (250 μ M and 1000 μ M) resulted in a stronger significant reduction of viable cells than TAU, except in one cell line (BxPC-3).

TAU inhibits proliferation of different cancer cell lines in a dose depended manor

BrdU proliferation test was used to investigate the anti-proliferative effect of TAU compared to TRD. The results, shown in Figure 3, indicate that TAU reduces cell proliferation significantly in a dose depended manor, starting with a concentration of 200 μ M. Treatment leads to values between $79.0 \pm 5.5\%$ (BxPC-3) and $31.6 \pm 5.0\%$ (HPAF II). The values of the proliferation rate at the highest concentration of TAU ranked between $18.4 \pm 3.4\%$ (HCT116) and $5.5 \pm 1.4\%$ (HPAF II). Comparing the results of TAU (500 μ M) and TRD (250 μ M), TRD caused a significantly higher decrease of cell proliferation in all treated cell lines, except HPAF II. There were no significant differences between the higher concentrations (TAU 2000 μ M and TRD 1000 μ M) in all tested cancer cell lines. Overall, these results indicate that TAU shows a dose depended effect on cell proliferation.

Taurultam induces apoptotic cell death in human cancer cells

FACS analyses were performed to compare the apoptotic and necrotic effects of both substances. All cell lines (AsPC-1, BxPC-3, HCT116 and SW480) were incubated with different concentrations of TAU and TRD for 24h. The results show a significant decrease of viable cells and an increase of apoptotic and necrotic cells in comparison to the untreated controls. The poorest response to TAU was observed in the cell line AsPC-1. The lower concentration of TAU (500 μ M) caused a significant decrease of viable cells $76.5 \pm 2.1\%$ and an increase of apoptotic cells ($14.3 \pm 0.6\%$) after 24h. A significant increase of apoptotic cells $13.4 \pm 0.7\%$ was also caused by

the highest concentration (2000 μ M), however without a reduction of viable cells (Figure 4). These results suggest a V-shape dose response effect among the cells. Likewise, the colon carcinoma cell line SW480 presented a V-shape dose effect (data not shown), where the lower tested concentration of TAU (500 μ M) led to a stronger response of the cells ($47.2 \pm 3.7\%$) than the higher (2000 μ M) concentration ($57.6 \pm 3.3\%$). Both concentrations achieved a significant increase of apoptotic cells without any increase of necrosis, values ranging between $49.5 \pm 3.7\%$ (500 μ M) and $36.1 \pm 3.7\%$ (2000 μ M). Interestingly, in BxPC-3 (data not shown) and HCT116 (Figure 4) an increase of necrotic cells in addition to apoptotic cells under treatment with TAU was observed, reaching maximum values of $11.3 \pm 0.3\%$ (500 μ M) necrotic cells in BxPC-3 and $23.1 \pm 2.5\%$ (2000 μ M) in HCT116.

Considering the results of the cell line BxPC-3 compared with the untreated control, TAU achieved a statistically significant reduction of viable cells in a dose depending manor, resulting in $45.1 \pm 0.4\%$ (2000 μ M). Furthermore, TAU implied a statistically significant increase of apoptotic cells, leading to results of $29.4 \pm 0.4\%$ (500 μ M) and $29.9 \pm 0.6\%$ (2000 μ M).

A significant effect on cell viability of HCT116 cells was caused by treatment with both concentrations of TAU (500 μ M and 2000 μ M) leading to an increase of apoptotic cells. A Maximum of $56.9 \pm 3.2\%$ (500 μ M) viable and $19.4 \pm 1.2\%$ (500 μ M) apoptotic cells was reached. Treatment with 2000 μ M TAU could not increase the pro-apoptotic effect, thus the dose response effect did not appear proportional. Comparative, two concentrations of TRD (250 μ M and 1000 μ M) were used because previous investigations showed that 250 μ M was the lowest concentration with a significant effect on human cancer cells and 1000 μ M TRD caused massive rise of apoptotic and necrotic cells [21].

Comparing the two lowest concentrations of TAU (500 μ M) and TRD (250 μ M), TAU was able to reduce the number of viable cells similar effective than TRD. This effect was especially determined by an increase of apoptotic cells. However, the concentration of 1000 μ M TRD was able to reduce the number of viable cells more effectively ($p < 0.001$) than TAU (2000 μ M) in all examined cell lines. Interestingly the amount of reduction of viable cells by TRD was especially caused by necrosis and less apoptosis (Figure 4) in contrast to treatment with TAU, which caused rather an increase of apoptosis than necrosis.

Analysis by the xCELLigence system

To evaluate the effects on cell proliferation and viability the real time, label free cell proliferation assay xCELLigence was performed. Figure 5 illustrates the results of the proliferative viability measurement by the system of the cell line AsPC-1 treated with various concentrations of TAU and TRD. A reduction of the CI of all tested concentrations was observed. Especially the concentration of 1000 μ M TRD showed an early massive drop of the cell index, not achieved by the concentration of 2000 μ M TAU. The concentrations of 200 μ M TAU and 100 μ M TRD caused a comparative drop of the CI. The concentrations 500 μ M and 2000 μ M TAU resulted in the poorest drop in the growth curve. All other tested cell lines showed a similar response to the treatment with TAU and TRD (data not shown).

Discussion

The anti-neoplastic effect of TRD was already shown in prior studies by cell viability assays like MTT [20,23] as well as by cell proliferation assays like BrdU [12,16,22] and FACS analysis

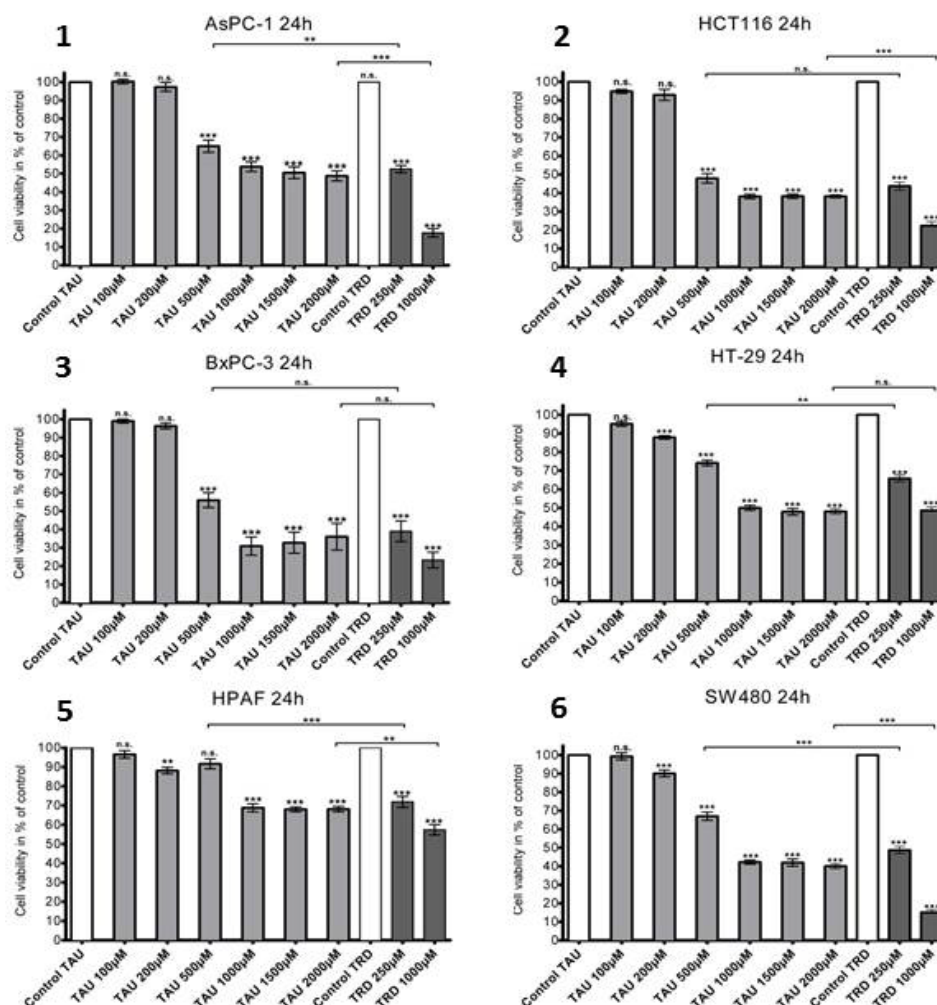


Figure 2: Results of the cell viability assay MTT treated with TAU and TRD. AsPC-1 (1), HCT116 (2), BxPC-3 (3), HT29 (4), HPAF II (5) and SW480 (6) were incubated with TAU (100µM, 200µM, 500µM, 1000µM, 1500µM and 2000µM) and TRD (250µM and 1000µM) for 24h. The results are expressed as mean value ± SEM of 8 independent experiments. Stars show differences between controls and compared TAU and TRD groups. The significance levels are graphically shown as follows: ***p ≤ 0.001, **p ≤ 0.01, *p ≤ 0.05, ns p ≥ 0.05 (one-way ANOVA followed by Tukey's post-hoc test).

[12,16,22,23]. However, there was no data in regards to the anti-neoplastic effect by its major breakdown product TAU on human cancer cells in the literature by now. This study was conducted to determine the anti-neoplastic activity of TAU on human pancreatic and colon cancer cell lines for the first time to elucidate whether the anti-neoplastic effect of TRD is mainly caused by its metabolite TAU. We were able to show, that TAU, as TRD, caused a significant reduction of viable cells in all analyzed cell lines (AsPC-1, BxPC-3, HCT116 and SW480) in a dose depending manor, determined by MTT assay. However, the results showed that TRD appeared to be more effective to reduce cell viability in pancreatic and colon cancer cell lines.

Similar findings were observed by cell proliferation assay with BrdU. Here, both substances showed a proportional dose response reduction of the cell proliferation (Figure 3). In comparison with the cytotoxic effect measured by MTT an anti-proliferative effect could be observed at a lower concentration of TAU in all analyzed cell lines. These findings suggest that the anti-proliferative effect of TAU might be slightly stronger than the cytotoxic effect. Furthermore, these

results match those observed in earlier studies, where a proportional dose response of cell proliferation was observed under treatment with TRD [22]. For a concentration of 250 µM TRD, a statistically stronger decrease of cell proliferation was observed compared to a concentration of 500 µM TAU. Even though, both substances showed an anti-proliferative effect, the findings clearly suggest that TRD seemed to have a stronger effect on the analyzed colon and pancreatic cancer cells.

Therefore, we conclude that the antineoplastic activity of TAU is less effective than the capacity of TRD, even when used in an adjusted quantity of 2 Mol. Hence, there is some evidence, that the metabolite and major breakdown product TAU might not be the only effective component of TRD.

A plausible explanation for these findings is that the antineoplastic effect of TRD is caused by methylol-containing species, which are already known to interact with bacterial and fungal cell walls thereby mediating the bactericidal effect of the substance [8,9]. Based on our results, we assume that these species could also generate the anti-neoplastic effect of TRD. On this context, the different efficiency

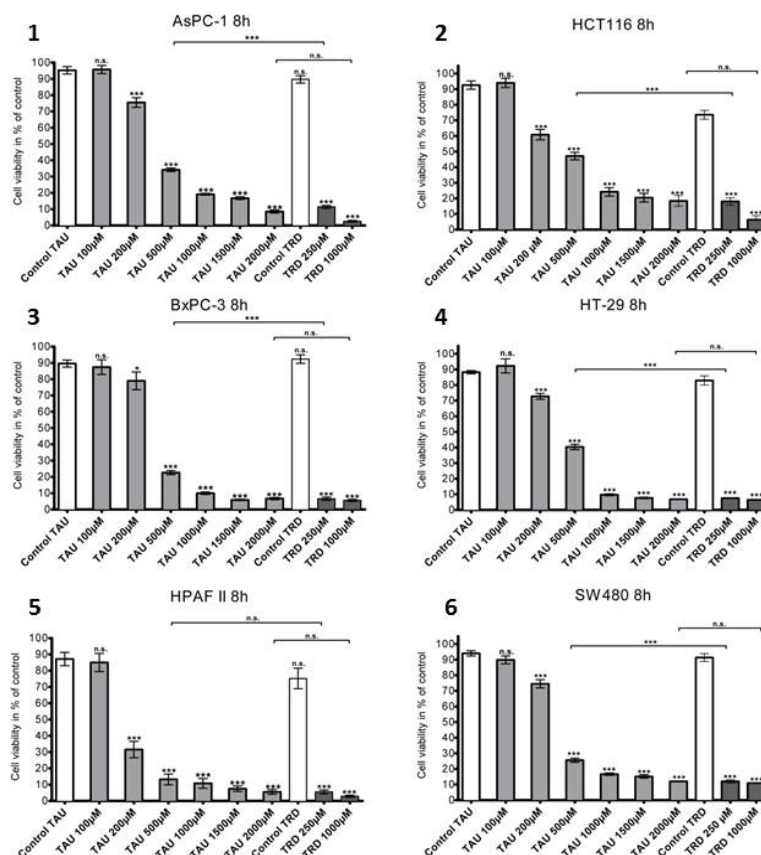


Figure 3: Results of the proliferation assay BrdU in different cancer cell lines with TAU and TRD. AsPC-1 (1), HCT116 (2), BxPC-3 (3), HT29 (4), HPAF II (5) and SW480 (6) were incubated with TAU (100µM, 200µM, 500µM, 1000µM, 1500µM and 2000µM) and TRD (250µM and 1000µM) for 8h and proliferation was measured by BrdU assay. The results are expressed as mean value ± SEM of 8 independent experiments. Stars show differences between controls and compared TAU and TRD groups. The significance levels are graphically shown as follows: ***p ≤ 0.001, **p ≤ 0.01, *p ≤ 0.05, ns p ≥ 0.05 (one-way ANOVA followed by Tukey's post-hoc test).

of both substances could be explained by the different amount of methylol-containing species released during hydrolysis (Figure 1), because during hydrolysis of 1 Mol TAU less methylol-containing species are released than during hydrolysis of 1 Mol TRD.

FACS analysis supported the results of both viability assays within this study. The lowest effective concentration of TAU at about 500 µM was observed among all analyzed cell. Surprisingly, differences were found between the dose response effects of TAU among the four treated cell lines analyzed by FACS analysis. In AsPC-1 and SW480 no direct dose response was observed. Here a concentration of 500 µM TAU implied a slightly bigger decline of cell viability whereas the higher (2000 µM) concentration was less effective (Figure 4). HCT116 cells showed a similar response within all tested concentrations of TAU. BxPC-3 was the only cell line, which was characterized by a proportional dose effect, observed after treatment with TAU. Our results are in a line with the findings of other studies, which also observed these different dose-response patterns between different cancer cell lines after treatment with TRD [13,21].

Contrary to our expectations, the results of this study show that the treatment with TRD resulted in a statistically significant (p<0.001) bigger rise of necrotic cells than the treatment with TAU. Treatment with TAU caused rather an increase of apoptosis than necrosis. We can only speculate about the reason of these findings; however the design

of our analysis could reveal a possible explanation. Apoptosis leads to caspases-depending cell destruction and further to phagocytosis of the apoptotic cells. In a cell culture setting, which lacks phagocytosis a secondary necrosis follows, which is characterized by the same appearance of primary necrosis [24]. In our in vitro studies there is no possibility of phagocytosis by inflammatory cells, which are not present in cell cultures. The marker used for necrosis (PI) could ultimately not differentiate between a substance-induced primary necrosis and secondary necrosis due to the lack of phagocytosis. Further work is required to clarify whether TRD or TAU lead to the induction of primary necrosis within tumor cells.

The xCELLigence system continuously monitors cell adhesion and cell proliferation for real time and label-free. It was used successfully in different studies to quantify the response of human cancer cells to anti-neoplastic substances [25,26]. The growth curves of the untreated controls showed characteristic profile of cell growth. In contrast cells treated with TAU and TRD showed the expected response among all cell lines, resulting in an obvious slope of the growth curves. These findings are in agreement with those observed in the MTT and BrdU assays as well as with the FACS analysis of our study. Again, the results advise that the treatment with TRD led to a stronger growth reduction compared to the treatment with TAU among all cancer cell lines.

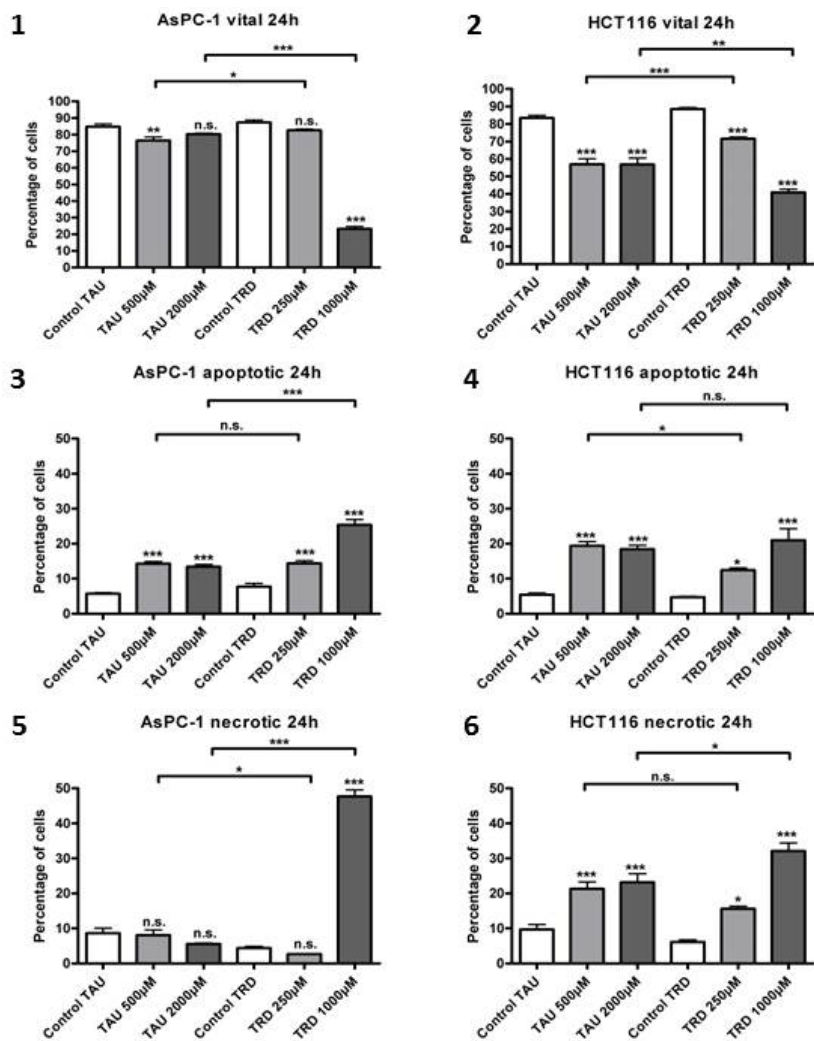


Figure 4: The effects of TAU (500µM and 2000µM) and TRD (250µM and 1000µM) on human pancreatic carcinoma cells after 24h. (1,3,5) AsPC-1, (2,4,6) HCT 116. The percentage of viable (1,2), apoptotic (3,4) and necrotic (5,6) cells was measured by FACS-Analysis using Annexin V-FITC and Propidiumiodid. Stars show difference between controls and compared TAU and TRD groups. The significance levels are graphically shown as follows: "" p ≤ 0.001, "" p ≤ 0.01, "" p ≤ 0.05, ns p ≥ 0.05 (one-way ANOVA followed by Tukey's post-hoc test).

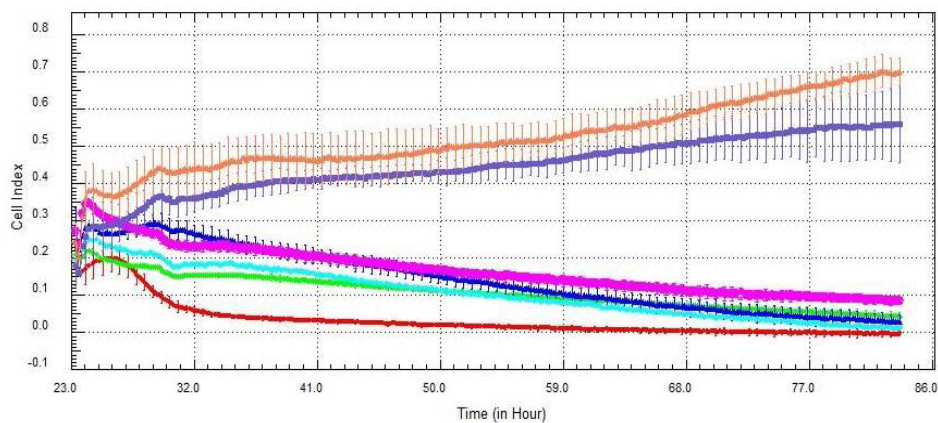


Figure 5: Cell proliferation and viability of AsPC-1 treated with TAU and TRD determined by the xCEL Ligenz system. Violet: control TAU (double distilled water), orange graph: control TRD (Povidon 5%), cyan: 200µM TAU, pink: 500µM TAU, blue: 2000µM TAU, green: 100µM TRD, red: 1000µM TRD).

Conclusion

TAU has an anti-proliferative and cytotoxic effect on different colon and pancreatic cancer cell lines. However, the results advise clearly, that TRD has a stronger effect on cancer cells than its metabolite TAU. These findings suggest that TAU does not cause the anti-neoplastic effect of TRD alone. Future trials should access the impact of the methylol-containing species on malignant cancer cells, which could be, based on the results of the current study, the possible mediators of the anti-neoplastic activity of TRD. The results of our study are also an important step towards extending our knowledge of the effectivity of TAU as an anti-neoplastic single ring structured molecule. In contrast to TRD, TAU shows a higher solubility in water, which would lead to higher concentrations and lower volume during therapeutic approaches. The analysis of TAU undertaken here provides the basis for further chemical modifications of TAU to increase the anti-neoplastic potential as a clinical relevant agent.

Authors' Contributions

MB and JB made substantial contributions to conception and design, acquisition of data as well as analysis and interpretation of data. AC made substantial contributions to conception and design. SH guided the xCelligence experiments. RP synthesized the analyzed agent. BMS, CB and WU revised the manuscript. All authors have read and approved the manuscript and take public responsibility for it.

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