Infections with viral strains belonging to the Flaviviridae family are responsible for important pathological consequences both in humans and in domesticated livestock. Bovine viral diarrhoea virus (BVDV) is the prototype virus of the Pestivirus genus (Collett et al., 1988) and has been adopted as a model for studying other members of the Flaviviridae family. BVDV has a replication cycle in common with the Hepacivirus genus, is replication efficient in cell culture and presents a lower biological hazard than other flaviviruses, such as yellow fever virus (YFV), Dengue virus or hepatitis C virus (HCV) (Zhong et al., 1998; Nam et al., 2001). Currently, there are few treatment options (interferon, ribavirin) for controlling Flavivirdae infections (Sentsui et al., 1998; Di Bisceglie et al., 2002). Inhibitors of viral specific targets are urgently needed and are actively being sought (Zhong et al., 1998; Baginski et al., 2000). Alternatively, inhibition of cell-specific targets (Zitzmann et al., 1999), including enzymatic steps that control intracellular nucleotide levels, are being explored (MacKiel et al., 2000).

Cells that are infected with actively replicating virus seem to require higher quantities and more rapid turnover of nucleotides than non-infected cells under the same conditions. The enzyme inosine-monophosphate dehydrogenase (IMPDH) catalyzes the rate-limiting step in the de novo synthesis of guanine nucleotides (Franchetti et al., 1999; Jain et al., 2001 and references therein). Inhibition of IMPDH reduces the level of intracellular guanine nucleotides required for adequate RNA and DNA synthesis. Therefore, IMPDH inhibitors have potential anti-proliferative, antiviral, and antiparasitic effects.

Introduction

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Currently, three IMPDH inhibitors are used clinically. The nucleosides ribavirin (Lau et al., 2002) and mizoribine (Yokota et al., 2002) are used as antiviral and immunosuppressive drugs, respectively, while the non-nucleoside agent mycophenolic acid (MPA) [a prodrug of mycophenolic acid (MPA)] is used as an immune-suppressant in many treatment regimens for the prophylaxis of organ rejection. MPA is a highly potent, selective, reversible, uncompetitive IMPDH inhibitor that binds to the enzyme’s co-factor...
binding site (Sintchak et al., 1996; Allison et al., 2000).

However, MPA undergoes extensive glucuronidation (up to 90%) in the liver to an inactive form. Subsequent de-glucuronidation and re-absorption in the gastrointestinal tract leads to toxic side effects, and a reduction of the clinical efficacy and therapeutic index of MPA (Franklin et al., 1996; Shipkova et al., 2001; van Gelder et al., 2003).

There are two common pathways to inhibit the IMPDH enzyme. The first is through analogues of the substrate, inosine-monophosphate (IMP), while the second is through analogues of the cofactor, nicotinamide adenine dinucleotide (NAD). Thus, nucleoside analogues need to be phosphorylated to the monophosphate form to act as substrate-type inhibitors (such as ribavirin-MP and mitoxantrone-MP). Cofactor-type inhibitors are (1) formed by metabolic conversion of nucleosides into NAD analogues (such as triazofurin-adenine dinucleotide; TAD; and benzamide riboside adenine dinucleotide, BAD), or (2) do not need activation, for example, MPA (which mimics the nicotinamide riboside moiety of NAD) or the synthetic bisphosphonate analogues of TAD, BAD and MAD (as described in this manuscript) (Tricot et al., 1992; Gharehbaghi et al., 1994; Pankiewicz et al., 1999a, 1999b, 2002).

In an attempt to find IMPDH inhibitors with improved clinical and antiviral profiles and with lower toxicity than the currently available clinical candidates, we evaluated a series of 15 compounds that are related to NAD. Three different classes of structures belonging to this group of compounds were prepared according to published procedures (Krohn et al., 1992; Pankiewicz et al., 1993). The IMPDH Kᵢ data in Table 1 were obtained from the literature (Pankiewicz et al., 2002) or references therein. Full compound characterization and degree of purity for all tested compounds have been published previously (Goldstein et al., 1991; Zatorski et al., 1995; Lesiak et al., 1997, 1998; Pankiewicz et al., 2002).

Virology

The cytopathogenic BVDV strain NADL (cpBVDV NADL) (Mendez et al., 1998) was plaque purified three times on Madin-Darby bovine kidney (MDBK) cell monolayers prior to large-scale virus stock preparation. Subsequently, this stock was titrated using a plaque assay essentially as described (Stuyver et al., 2003). Briefly, MDBK monolayers (3×10⁵ cells per 20 mm-diameter well) were infected with 100 µl of 10-fold serial dilutions of cpBVDV suspended in medium. One hour after infection the inoculum was removed and the monolayers were washed once with MDBK medium. One ml of MDBK medium containing 196 methylcellulose was added to the monolayers. Plaques were counted at 48 to 72 h post-infection.

MDBK cells (3×10⁵/well) were seeded in 96-well plates and incubated for 1 h (for tests with exponentially growing cells) or 72 h (for tests with confluent monolayers). The supernatant was removed and the cpBVDV NADL was added to the cells at a multiplicity of infection (MOI) of 0.02. Following a 45 min incubation at 37°C, the cells were washed twice with media, after which fresh media with or without the test compound was added. After 24 h (in exponentially growing cells) or 72 h (on confluent cells) of incubation the cell supernatant fluids were collected, clarified by centrifugation, and viral RNA was extracted.

Materials and methods

Compounds

Interferon (IFN)-α2a (Roferon-A, Hoffmann-La Roche, NJ, USA) was included as positive control in all assays. Chemical structures of compounds tested in this paper are shown in Figure 1. Tiazofurin and benzamide riboside were prepared according to published procedures (Krohn et al., 1992; Ramasamy et al., 2000). MPA (6) was kindly provided by Dr Takashi Tsuji of Ajinomoto, Inc., Japan. The compounds of syntheses 8, 7–9, 11 and 12 was published previously (Jones et al., 1971; Pankiewicz et al., 2002). Compounds 10 and 13 were prepared by sodium chlorite oxidation of the corresponding aldehydes 9 and 12 (Bal et al., 1981; Lindgren et al., 1995). The IMPDH Kᵢ data in

Table 1 were obtained from the literature (Pankiewicz et al., 2002) or references therein. Full compound characterization and degree of purity for all tested compounds have been published previously (Goldstein et al., 1991; Zatorski et al., 1995; Lesiak et al., 1997, 1998; Pankiewicz et al., 2002).

Q-RT-PCR for the BVDV NS5B region

Virus in the cell supernatant was extracted using the vacuum protocol of the Q™Amp Viral RNA Mini Kit (Quagen Inc, Valencia, Calif., USA). Viral RNA was eluted from columns in 60 µl, and 5 µl was used in the Q-RT-PCR (TaqMan 7700 Chemistry, Applied Biosystem, Foster City, Calif., USA) as described (Stuyver et al., 2002). As this Q-RT-PCR technology measures the threshold cycle (Ct) of PCR-related fluorescence that is significantly different from background fluorescence, all efficacy data were deduced from those Ct values (Stuyver et al., 2002). In a 100%-efficient PCR experiment, a 2-log reduction of viral RNA (ECₑ) corresponded with a reduction of 3.3 Ct.

Cytotoxicity determinations

MDBK cells were seeded in duplicate in 96-well plates in the absence or presence of increasing concentrations of test compounds (threelfold dilutions). After 3 days of incubation, cell viability was measured using the CellTiter 96®

2

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Figure 1. Chemical structures of compounds used in this study
AQueous One Solution Cell Proliferation Assay (Promega, Madison, Wisc., USA), reading at 490 nm. The CC50 value (concentration of compound required to reduce cell viability by 50%) was calculated. For experiments that required a confluent monolayer of MDBK cells, test compounds in fresh media were added 3 days after initial seeding of 5×10⁴ cells/well.

Results

Relation between plaque forming units (pfu) and Q-RT-PCR

The cpBVDV virus stock was titrated using traditional plaque assays and found to contain 6×10⁶ pfu/ml. Serial 1-log dilutions of viral quantities from 6000 to 0.06 pfu were extracted (in triplicate) for viral RNA and amplified in the Q-RT-PCR protocol (in duplicate) (Figure 2). These results show that one pfu corresponds with a Ct value of approximately 30 in currently described protocol (see Materials and methods). Since we were able to obtain amplification signals below one pfu, this illustrates that not all the viral RNA present in the inoculum extract is infectious. The 5-log standard curve had a lower limit of reliable quantification at about Ct 17, and the upper limit of quantification was limited at about Ct 34. However, in the approaches described in this manuscript, a standard curve methodology was not used. Instead, the antiviral potencies for drug evaluation for the following reasons: (1) there was a 4-log dynamic range that was superimposable on the previously generated standard curve; and (2) a 4-log dynamic range allows the calculation of an EC99.99 value, which is sufficiently sensitive for drug evaluations in vitro.

Dynamics of BVDV RNA production in MDBK cell supernatant

The dynamics of BVDV production were evaluated both on MDBK cells growing exponentially and on a confluent cell monolayer. For the exponentially growing cells, supernatant fluids of exponentially growing MDBK cells by Q-RT-PCR

Figure 2. Standard curve showing relation between plaque forming units and Q-RT-PCR Ct values

Figure 3. Relative quantification of BVDV RNA in supernatant fluids of exponentially growing MDBK cells by Q-RT-PCR

The amount of virus produced was measured over a 4-day time course in the presence or absence of inhibition. A. no-drug control; B. IFN-α-2a at 10 IU/ml; C. IFN-α-2a at 33 IU/ml; D. ribavirin at 10 µM; E. ribavirin at 33 µM. Shaded area denotes values outside the linear range of standard curve as determined in Figure 2. Samples with Ct values outside the linear range (at the lower and at the higher end) can be detected, but their correct quantification could not be guaranteed.

The cpBVDV virus was inoculated into either exponentially growing or confluent monolayers of MDBK cells (see Materials and methods). Since we were able to obtain amplification signals below one pfu, this illustrates that not all the viral RNA present in the inoculum extract is infectious. The 5-log standard curve had a lower limit of reliable quantification at about Ct 17, and the upper limit of quantification was limited at about Ct 34. However, in the approaches described in this manuscript, a standard curve methodology was not used. Instead, the antiviral potencies for drug evaluation for the following reasons: (1) there was a 4-log dynamic range that was superimposable on the previously generated standard curve; and (2) a 4-log dynamic range allows the calculation of an EC99.99 value, which is sufficiently sensitive for drug evaluations in vitro.

For infections on the confluent cell monolayer, an identical set of experiments was performed (Figure 4). Cell supernatant was collected for four consecutive days, and viral RNA was quantified. The total amount of virus produced at day 4 was within the detection range of the standard curve (less than 5 log of virus), and thus significantly less than in the exponentially growing cells. In these experiments, the amount of virus produced after treatment with 100 IU/ml of IFN-α-2a remained below the reliable limit of quantification (which was set at Ct 34—the lower end of...
Growing cells. If the EC90 exponential was less than 40, two different stages of MDBK cells, the antiviral potential way purine biosynthetic. Cells that maintain viability primarily through salvage pathway pools, but practically no toxicity on confluent nucleotide biosynthesis. These compounds showed toxic effects in exponentially growing cells with high demands of nucleotide pools, but practically no toxicity on confluent cells that maintain viability primarily through salvage pathway purine biosynthesis.

Because of the different toxicity observations on the two different stages of MDBK cells, the antiviral potential of the compounds was evaluated first on exponentially growing cells. If the EC90 exponential was less than 40 pM, the compounds were tested in confluent cells. Compounds were tested over a range of concentrations (1–100 µM, threefold dilutions) for antiviral efficacy and the EC90 values were determined (Table 1). Besides ribavirin and MPA, five other compounds (4, 5, 7, 8, and 20, Table 1 and Figure 1) had EC90 values of less than 10 µM in both assays. A selectivity index (SI) could be calculated by dividing the toxicity data (CC50) by the efficacy data (EC90). C2-MAD (20) was the only co-factor type analogue that showed a preferable SI on both exponential and confluent cells. Surprisingly, compound 7, and to a lesser extent compounds 5, 8, and 10 (all four are modifications of MPA), showed extremely potent inhibition of virus production and a toxicity pattern more favorable than MPA.

The antiviral activity and related toxicity could be prevented for all compounds by adding 100 µM guanosine to the incubation media (data not shown). The Kd data for the human IMPDH enzyme is provided in Table 1 (if known and available).

**Discussion**

The aim of this study was to determine the anti-BVDV and toxic effects of a series of compounds that are related to the IMPDH inhibitors MPA and ribavirin. D-ribavirin and micophenolate (compounds 1a and 2) require activation to the monophosphate form and act as a substrate inhibitor and transition-state inhibitor (Kerr et al., 1997), respectively, while tofacitinib and benzamide riboside (compounds 3 and 4) require activation to the NAD form before they can act as IMPDH co-factor-type inhibitors. L-ribavirin (compound 1b) was recently shown to be potentially important for the treatment of HCV as a nucleoside with immunomodulating capacities (Rossi et al., 2001).

However, in the BVDV system, only the antiviral properties could be evaluated. D-ribavirin showed potent inhibition in BVDV production (EC90>4 µM), the l-ribavirin counter part did not show any antiviral activity (EC90=100 µM). As l-ribavirin did not show any toxicity in the 3 days MDBK toxicity assay, it is most likely not recognized as a substrate for activation by the bovine cellular enzymes. Likewise, micophenolate (compound 2) was not toxic, but also not active as an antiviral. However, its Kd on the human IMPDH is 0.004 µM, making it one of the most potent IMPDH inhibitors. This again suggests that micophenolate is not phosphorylated in bovine cells, or that inhibition of IMPDH alone is not sufficient for antiviral activity.

Compounds 5 to 20 do not need activation. Three different classes are recognized: (1) compounds 5–13, as derivatives of MPA (compound 6), most probably mimic the nicotinamide-moiety of the cofactor and bind into the enzyme cofactor pocket; (2) compounds 14–17 are dinucleoside-cofactor type analogues and mimic the NAD structure; and (3) compounds 18–20 are novel cofactor-type analogues, in which the mycophenolic moiety replaces the nicotinamide riboside part of NAD.
ethylenebis(phosphonate) analogue (–P-CH2-P–), resulting in a pro-
drug bond was chemically stabilized by synthesis of a meth-
ester or alcohol moiety increased with chain increasing length
in a par-
toxic environment. However, one can argue that the
apparent for several compounds. The 24 h antiviral assay
selectivity window as potential antiviral was
important requirement for antiviral activity. However,
changing the –OH (or carboxylate) group to –O-CH3 (
the corresponding methyl ester) increased the antiviral
potency but not the toxicity in confluent cells.

Three MAD-type of inhibitors with variable chain
length were tested (18–20). In the confluent cells, a pro-
nounced decrease in activity was observed with increasing
chain length (18 >> 19 >> 20).

For most compounds, the anti-BVDV activity paralleled
the cytocidalcytotoxicity in a 3-day assay. Compounds that were not
toxic to MDBK cells were also not active as antiviral
agents. However, as indicated by the SI on confluent cells
(Table 1), a selectivity window as potential antiviral was
apparent for several compounds. The 24 h antiviral assay
combined with the Q-RT-PCR technology allowed the
antiviral evaluation of these compounds in a practically
non-toxic environment. However, one can argue that the
cells, immediately after exposure to these classes of com-

Table 1. Anti-BVDV and cellular toxicity effects of MPA analogues

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*All concentrations in µM.

Stuyver et al.
pounds, received a toxic or cytostatic signal, but the conse-
quences of these signals were only visible after a 3-day
exposure. Alternatively, it was shown that confluent cell
monolayers could be used for meaningful antiviral testing.
C2-MAD (20) was found to be 1-log less potent than
MPA (Ki=0.3 µM versus Ki=0.035 µM) against the human
IMPDH enzyme. In human NsA, MPA is rapidly metabolized
to the inactive glucuronide, and as much as 90% of the drug
circulates in this inactive form (Franklin et al., 1996).
Modification of the phenolic-hydroxyl group of MPA with a fluo-
teine group to prevent the glucuronida-
tion resulted in inactive compounds (Franklin et al., 1996).
In contrast to MPA, C6-MAD and C2-MAD (18 and 20)
were found to be resistant to glucuronidation in vivo (Lesiak et al., 1998). These results indicate that if MAD
analogues are not glucuronidated in vivo, they would be
expected to have better therapeutic potential than MPA.

In conclusion, we have identified previously unreported
IMPDH inhibitors that also have anti-BVDV activity
(C6-MPAlc, C6-MPA- Me, C7-MPAlc, C4-MPAlc, C4-
MPA, and C2-MAD (20). The full spectrum of activ-
ity against other viruses for these compounds is in progress.

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References

mechanisms of action. Antimicrobial Agents and
Chemotherapy 44: 115–118.
Baginski SG, Pesovic VC, Sopel M, Sun SC, Bonten CA,
Chandrasekhar SA, Rice CM & Collett MS (2000) Mechanism of
action of a purinergic antiviral compound. Proceedings of the
National Academy of Sciences USA 97(9): 4971–4976.
Bal BS, Chikone W & Pinkin HH (1981) Oxidation of alpha,
Collett MS, Anderson DK & Retzel E (1988) Comparisons of the
potency and selectivity of benzamide riboside, a new inhibitor of IMP dehy-
drogenase, with thiouracil and benzimidazole. Journal of Medicinal
Chemistry 31: 2533–2538.
Lesiak K, Watanabe KA, Majumdar A, Seidman M, Vanderven K,
Goldstein BM & Paull KD (1992) Cytotoxicity of a new IMP dehydro-
genase inhibitor VX-497: a comparison with ribavirin and demonstration of antiviral
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