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Natural Inhibitors of Poly(ADP-ribose) Polymerase-1

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Abstract Poly(ADP-ribose) polymerases (PARPs) are enzymes that catalyze the transfer of ADP-ribose units from β-nicotinamide adenine dinucleotide (NAD^+) to acceptor proteins. PARP-1 is responsible for more than 90 % of protein poly-ADP-ribosylation in the brain and may play a role as a molecular switch for cell survival and death. The functional roles of PARP-1 are largely mediated by its activation after binding to damaged DNA. Upon binding, PARP-1 activity increases rapidly and cleaves NAD^+ into ADP-ribose and nicotinamide. Increased activity of PARP-1 can promote DNA repair and its interaction with several transcription factors, whereas hyperactivation of PARP-1 can result in poly(ADP-ribose) accumulation and depletion of NAD^+ and ATP which may lead to caspase independent apoptotic or necrotic cell death, respectively. Excessive PARP-1 activity has been implicated in the pathogenesis of numerous clinical conditions such as stroke, myocardial infarction, inflammation, diabetes, and neurodegenerative disorders. Therefore, it is not surprising that the search for PARP-1 inhibitors with specific therapeutic uses (e.g., brain ischemia, cancer) has been an active area of research. Beyond medicinal uses, naturally occurring PARP-1 inhibitors may also offer a unique preventative means at attenuating chronic inflammatory diseases through dietary supplementation. This possibility has prompted research for specific, naturally occurring inhibitors of PARP-1. Though fewer investigations focus on identifying endogenous inhibitors/modulators of PARP-1 activity in vivo, these activities are very important for better understanding the complex regulation of this enzyme and the potential long-term benefits of supplementation with PARP-1 inhibitors. With this in mind, the focus of this article will be on providing a state-of-the-science review on endogenous and naturally occurring compounds that inhibit PARP-1.

Keywords Poly(ADP-ribose) polymerase · PARP · PARS · Endogenous inhibitor · Naturally occurring inhibitor · Mode of action

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Introduction

Poly(ADP-ribose) polymerases (PARPs) comprise a family of enzymes that catalyze the transfer of ADP-ribose units from β-nicotinamide adenine dinucleotide (β-NAD^+ or NAD^+) to acceptor proteins. The biological roles of polymers of ADP-ribose [poly(ADP-ribose) or (PAR)] and poly-ADP-ribosylation of proteins are diverse. The first discovered and best characterized among PARPs is PARP-1 (EC 2.4.2.30). PARP-1 is a conserved nuclear zinc metalloprotein that functions as a DNA nick sensor and signaling molecule. This protein is comprised of three primary functional domains, which consist of an N-terminal DNA-binding domain, including a nuclear localization signal, a central automodification domain, and a C-terminal catalytic domain [1]. The DNA binding domain contains two zinc-

finger motifs that facilitate binding to both single- and double-stranded DNA breaks. The functional roles of PARP-1 are largely mediated by its activation after binding to damaged DNA. Upon binding, PARP-1 activity increases rapidly and cleaves NAD^+ into ADP-ribose and nicotinamide. Linear and branched PARs are synthesized and covalently attached to a number of acceptor proteins, including histones and PARP-1 itself. The in vivo half-life of PAR is less than 1 min. PAR is catabolyzed by poly(ADP-ribose) glycohydrolase and, to a much lesser extent, by ADP-ribosyl protein lyase [2].

Under normal and mild stress conditions, PARP-1 acts as a defense mechanism by detecting DNA strand breaks and nicks, resulting from the constant insult of reactive oxidative species that arise from normal aerobic respiration [3, 4]. PARP-1 is involved in base excision repair pathways and plays an important role in regulation of transcription. Activation of PARP-1 leads to the formation of PAR which now is recognized as a novel signaling molecule that plays an important role in the regulation of transcription factors and other proteins which contain specific PAR domains. More severe injuries such as ischemia-reperfusion and inflammation can hyperactivate PARP-1, leading to an energy crisis in the cell due to the rapid depletion of NAD^+ and ultimately ATP [5–11]. Moreover, elevated levels of PAR may also alter mitochondrial permeability, leading to release of apoptosis inducing factor (AIF). Translocation of AIF to the nucleus may activate caspase independent cell death [12, 13]. PARP-1 inhibition has been shown to ameliorate these effects [14, 15], including those caused by chemical insults that act via free radical mechanisms [16–18].

Biological roles of PARP-1 were established largely from experiments employing its inhibitors. In the beginning, these were mostly endogenous or naturally occurring compounds such as nicotinamide, thymidine, or theophylline [19]. Most of these compounds were, however, found to affect other biological processes. Therefore, in order to target PARP-1, there was a need to identify more specific, not necessarily natural, PARP-1 inhibitors. In 1980, Purnell and Whish [20] reported that several synthetic 3-substituted benzamides were much more potent and specific inhibitors of PARP-1 in vitro than known endogenous and naturally occurring compounds. In addition, Rankin et al. [21] showed in 1989 that several benzamide derivatives are potent and specific PARP-1 inhibitors in vitro and in vivo. Historically, 3-aminobenzamide was the most favored PARP-1 inhibitor and served as an indispensable tool in studies aimed at elucidating the biological roles of poly-ADP-ribosylation. However, at least at high concentrations, 3-aminobenzamide and other benzamides have considerable adverse side effects in vivo. It wasn't until 1992 when Banasik et al. [22] showed that members of several classes of compounds, including many endogenous and naturally occurring ones, were potent and specific PARP-1 inhibitors in vitro. Other investigators proved using animal models that PARP-1 inhibitors are beneficial in various pathological conditions, including ischemia [15, 23–26], diabetes [27, 28], or neurodegenerative disorders [29–32]. In cancer therapy, PARP-1 inhibitors are in clinical trials (Phase I–III) and, thus far, offer promising results in the treatment of melanoma and breast cancers [33, 34]. Therefore, PARP-1 inhibitors may have direct therapeutic use in some of the most challenging areas of modern medicine. This has prompted intensive search for specific inhibitors of PARP-1, mainly synthetic compounds or derivatives of natural compounds due to concerns over patent infringement.

Since the breakthrough discovery by Banasik et al. [22], several new endogenous and naturally occurring regulators of PARP-1 have been found, which include antibiotics (e.g., tetracyclines), vitamins (e.g., vitamin D_3), etc. [35–37]. This review will focus on the state of science for endogenous and naturally occurring compounds that inhibit PARP-1.

Mode of Action for PARP-1 Inhibition

The mode of action for many of the endogenous and naturally occurring PARP-1 inhibitors is unclear, and discrepancies exist in the literature. The compounds documented as competitive inhibitors with respect to NAD^+ include caffeine [38], 2'-deoxythymidine 5'-monophosphate [39], formycin B [40, 41], 1-methyladenine [40], NADH [42, 43], NADP [44], nicotinamide [28, 38, 42–49], polydeoxythymidylate [43], showdomycin [40], taurine [28], theobromine [38], theophylline [38, 50], and thymidine [38, 39, 43, 44, 47, 48]. However, Banasik et al. [22] showed that most inhibitors investigated, including nicotinamide [51], exhibited mixed-type inhibition with respect to the substrate NAD^+ at micromolar concentrations (Fig. 1a). This discrepancy may be due to differences in reaction conditions (e.g., inhibitor concentration and/or enzyme preparations). For example, xanthurenic acid (at 50 and 100 μM) proved to exhibit competitive inhibition with respect to NAD^+ (Fig. 2) [22]. A mixed-type inhibition was shown, however, at 200 μM (not shown), which resembled the dual inhibitory action of arachidonic acid, i.e., competitive inhibition at 50 μM with mixed-type inhibition at 100 μM (Fig. 1b) [51]. Mixed-type inhibition was previously reported for a natural nucleotide, diadenosine 5',5'''-p^1,p^4-tetraphosphate (Ap4A), a ligand of a subunit of DNA polymerase α [52, 53]. ATP [54], two 2',5'-oligoadenylates, A2'pA2'pA [55] and pppA2'pA2'pA [55, 56], and coumarin [57] have been documented as noncompetitive inhibitors.

Natural Inhibitors of PARP-1

Some mammalian endogenous and naturally occurring compounds have been shown to inhibit PARP-1 activity in vitro

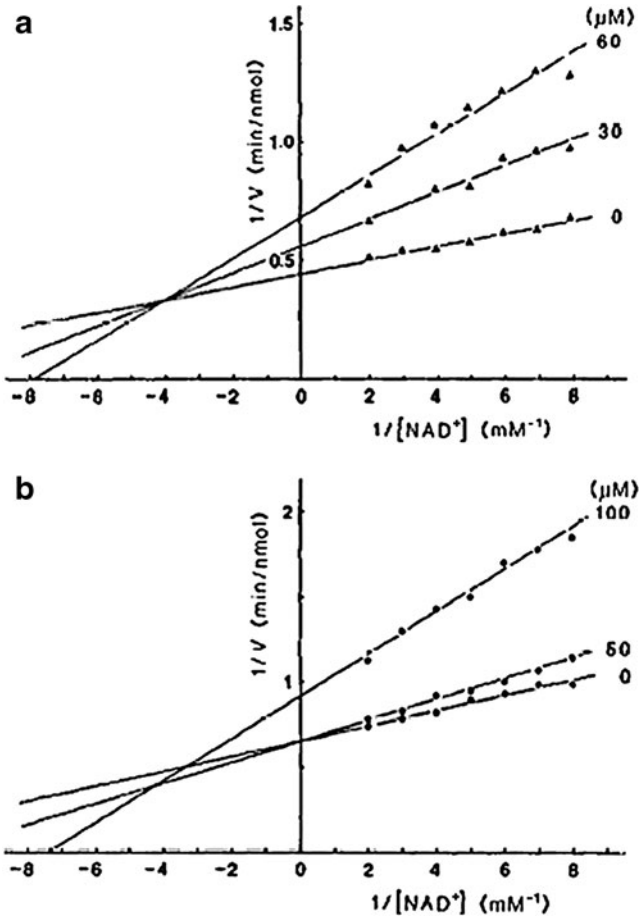

Fig. 1 Standard Lineweaver–Burk plots showing the mixed-type inhibition of PARP-1 activity by nicotinamide (**a**) and, depending on concentration used, competitive and mixed-type inhibition by arachidonic acid (**b**) (adapted from [51])

and/or in vivo. Tables 1 and 2 list endogenous and naturally occurring inhibitors, respectively, for which IC_{50} (the concentration that causes 50 % inhibition) or EC_{50} (half maximal effective concentration), and/or inhibition constant (*K*i) value(s) have been determined.

The Early PARP-1 Inhibitors

Nicotinamide is a critical part of NAD^+ and a byproduct of ADP-ribosylation reactions. Because of this, nicotinamide was quickly established as a PARP-1 inhibitor, and as noted previously, most of the early research in this field has utilized this compound [42, 44–46, 48, 49, 58–69]. Other inhibitors used previously are thymidine [39, 44, 48, 49, 61, 64–67], thymine [61, 66], and theophylline [49, 64, 67, 70]. Most of these compounds also affect other biological processes. For example, nicotinamide is an inhibitor of enzymes, which use NAD^+ as substrate like ADP-ribosyltransferases, NAD^+ glycohydrolases, or sirtuins and cyclic-AMP phosphodiesterase, and several proinflammatory cytokines. It is a substrate for nicotinamide *N*-methyltransferase, nicotinamide amidohydrolase, and nicotinic acid/nicotinamide adenylyltransferase. Nicotinamide (3-pyridinecarboxamide) is the precursor of NAD^+, can be directly utilized by cells to synthesize NAD^+, and leads to elevated concentrations of pyridine nucleotides. PAR, another byproduct of poly-ADP-ribosylation reaction, has also been shown to inhibit polymer synthesis in vitro [71].

NAD^+, an essential cofactor for several oxidoreductases and substrate for NAD^+-consuming enzymes, is a central molecule in cellular metabolism and participates in a wide range of biological processes, including energy supply, cellular resistance to stress or injury, and longevity. Since NAD^+ is the substrate for PARP-1, its concentration in the cell will affect PARP-1 activity. In addition, it has been established that NAD^+ concentration can affect the degree of PARP-1 inhibition in vitro [72]. NADH [42] and NADP [44] have also been shown to inhibit PARP-1. NAD^+ is synthesized de novo from tryptophan or in salvage pathways by recycling compounds such as nicotinamide back to NAD^+.

Tryptophan-Related Compounds

Interestingly, xanthurenic acid and kynurenic acid, metabolites from tryptophan catabolism, inhibit PARP-1 in vitro

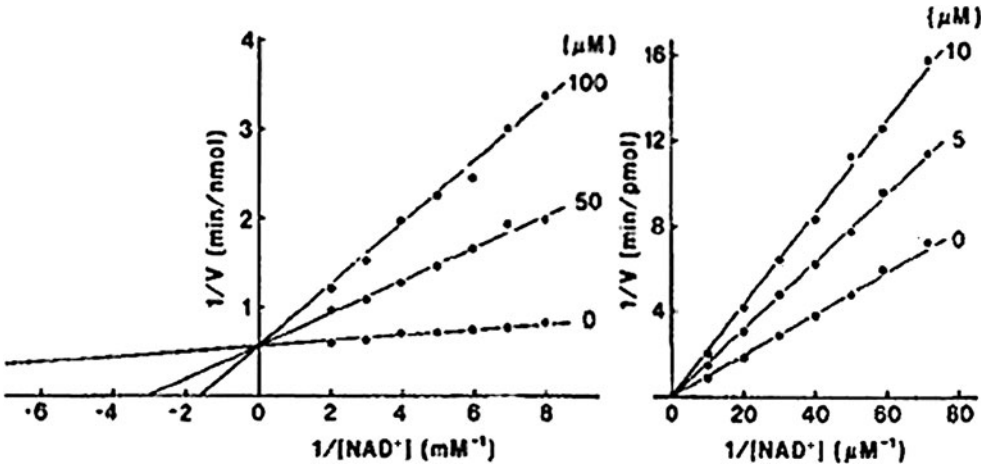

Fig. 2 Standard Lineweaver–Burk plot showing the competitive inhibition of PARP-1 activity by xanthurenic acid. The final concentrations of DMSO in reactions with micromolar and nanomolar NAD + were 0.5 % (adapted from [22])

Table 1 PARP-1 inhibition values (μM) of select mammalian endogenous compounds

Compound	K_i	IC_{50}	Reference
A2'pA2'pA	50	–	[55]
A2'pA2'pA	100[a]	–	[56]
Ap4A	5.1	~10[a]	[52]
Ap4A	–	>400	[52]
Ap4A	7.7	–	[53]
Arachidonic acid[b]	–	44	[51]
ATP	4,000	–	[54]
1α,25-Dihydroxyvitamin D_3	–	~3	[37]
Hypoxanthine	–	1,700	[21]
Hypoxanthine	–	>200	[98]
Hypoxanthine	–	~1,000[c]	[74]
Kynurenic acid[b]	–	670	[73]
γ-Linolenic acid[b]	–	120	[22]
1-Methyladenine	226.6	–	[40]
1-Methylnicotinamide	–	1,700	[21]
1-Methylnicotinamide	–	3,800	[73]
NADH	55	–	[42]
NADP	460	–	[44]
Nicotinamide	52	–	[45]
Nicotinamide	20	–	[46]
Nicotinamide	~14	–	[62]
Nicotinamide	14.3	–	[48]
Nicotinamide	5.7	–	[99]
Nicotinamide	50	–	[42]
Nicotinamide	5.6	–	[100]
Nicotinamide	23	–	[44]
Nicotinamide	–	~100	[69]
Nicotinamide	15	–	[101]
Nicotinamide	13.0	–	[38]
Nicotinamide	–	31	[21]
Nicotinamide	–	210	[51]
Nicotinamide	–	~2,000[c]	[74]
Nicotinamide	–	210	[28]
Norharman hydrochloride	–	4,700	[102]
Oleic acid[b]	–	82	[22]
Palmitoleic acid[b]	–	95	[22]
L-α-Phosphatidyl-DL-glycerol, distearoyl[d]	–	<830	[–*]
pppA2'pA2'pA	5[a]	–	[56]
pppA2'pA2'pA	20	–	[56]
pppA2'pA2'pA	5	~10	[55]
Pyridoxal 5-phosphate[b]	–	4,250	[51]
Taurine	–	320	[28]
Thymidine	32.5	–	[48]
Thymidine	140	–	[44]
Thymidine	25	–	[101]
Thymidine	13.3	–	[38]
Thymidine	–	43	[21]
Thymidine	–	180	[22]
Thymine	–	290	[22]
3,5,3'-Triiodothyronine	–	0.001[e]	[82]
Vitamin A aldehyde[b]	–	450	[51]
Xanthurenic acid[b]	–	190	[73]

[a] Histone poly-ADP-ribosylation

[b] 2 % (final) (DMSO)

[c] EC_{50}

[d] 10 % (final) DMSO, the considerable variation in IC_{50} or K_i values reported for individual compounds indicates that the experimental conditions and enzyme preparations may profoundly affect these values [19]

[e] In isolated male rat liver nuclei; IC_{50} value for PARP-1 purified from calf thymus is 1 aM

*Unpublished data, Banasik et al.

[22, 73]. Carboline compounds affect the PARP-1 activity in a complex way [73]. 3-Amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*] indole (Trp-P-1) is a fairly strong inhibitor, whereas 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole (Trp-P-2) is an activator at around 1 mM, but it is inhibitory at higher concentrations [73]. These two γ-carbolines are pyrolytic products of tryptophan and are known to be mutagenic and carcinogenic. Another heterocyclic amine, 2-amino-3-methyl-9*H*-pyrido[2,3-*b*]indole (MeAαC), present in various foods and in the environment, is also inhibitory to PARP-1 in vitro.

Purines

Virág and Szabó [74] have shown that several purines (hypoxanthine > inosine > adenosine) dose-dependently inhibit PARP-1 activation in peroxynitrite-treated RAW mouse macrophages as well as inhibit the activity of purified enzyme. The authors suggested that purines may serve as endogenous inhibitors of PARP-1 [74]. Some other purines (e.g., biophylline, caffeine, hypoxanthine, 1-methyladenine, 1-, 3-, 7-, 8-methylxanthine, paraxanthine, theobromine, theophylline) have also been documented as PARP-1 inhibitors (Tables 1 and 2). ATP, at physiological cellular concentrations, preferentially inhibits PARP-1 automodification and, to a lesser degree, poly-ADP-ribosylation of histones in vitro [54].

Diadenosine Polyphosphates

Naturally occurring diadenosine polyphosphates, extracellular mediators controlling numerous physiological effects, have a chain length varying from three to six phosphate groups (Ap_nA with n=3 to 6). Tanaka et al. [52] demonstrated that these compounds are strong inhibitors of histone H1 ADP-ribosylation by purified bovine thymus PARP-1. It

Table 2 PARP-1 inhibition values (μM) of select naturally occurring compounds

Compound	K_i	IC_{50}	Reference
Apigenin[a]	–	<1,500	[102]
$AsNaO_2$ (sodium arsenite)	–	10	[93]
Biophylline	–	>200	[98]
Coumarin	4.7	–	[57]
Coumarin[a]	–	2,800	[22]
Coumermycin A_1	–	~250	[19]
Caffeine	–	~1,000	[38]
Caffeine	244	–	[38]
Caffeine	–	1,400	[21]
Caffeine	–	>200	[98]
1,7-Dimethylxanthine	–	15	[98]
Flavone[a]	–	22	[22]
Formycin B	68.9	–	[40, 41]
Formycin B	75	–	[41]
Harmine hydrochloride	–	<3,500	[102]
4-Hydroxycoumarin[a]	–	570	[22]
Juglone[a]	–	250	[22]
Lawsone[a]	–	330	[22]
Linoleic acid[a]	–	48	[51]
α-Linolenic acid[a]	–	110	[51]
MeAαC[a]	–	<3,300	[–*]
1-Methylxanthine	–	145	[98]
3-Methylxanthine	–	115.2	[98]
7-Methylxanthine	–	172.3	[98]
8-Methylxanthine	–	>200	[98]
Novobiocin	–	2,200	[22]
Plumbagin[a]	–	700	[22]
Reserpine[b]	–	790	[73]
Showdomycin	107.8	–	[40]
Theobromine	15.2	–	[38]
Theobromine	–	110	[21]
Theobromine	–	160.2	[98]
Theophylline	30.0	–	[70]
Theophylline	29.8	–	[38]
Theophylline	–	46	[21]
Theophylline	–	194.8	[98]
Trp-P-1	–	220	[73]
Trp-P-2[a]	–	2,200	[73]
Vitamin K_1[b]	–	520	[51]
$ZnCl_2$	–	10	[90]
$ZnCl_2$	–	77	[21]

[a] 2 % (final) DMSO

[b] 10 % (final) DMSO, the considerable variation in IC_{50} or Ki values reported for individual compounds indicates that the experimental conditions and enzyme preparations may profoundly affect these values [19]

*Unpublished data, Banasik et al.

should be noted that Ap4A functions as an acceptor for ADP-ribose in a PARP-1 reaction in vitro [75]. Possible in vivo regulation of PARP-1 activity by 2',5'-oligoadenylates has been also suggested [55, 76]. Recently, it has been found that adenosine thiamine triphosphate at 10 μM almost completely inhibited the activity of recombinant PARP-1 [77]. The authors speculated that the beneficial impacts of high-dose thiamine treatment on diabetic complications could result, to some extent, from PARP-1 inhibition by thiamine derivatives.

Vitamins and Vitamin-Like Substances

Mabley et al. [37] have found that the active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3, dose-dependently inhibited PARP-1 in a cell-free assay, with 40 % inhibition being observed at 0.1 μM and 80 % at 1 μM. It should be noted that other vitamins or their precursors (vitamin A aldehyde > vitamin K_1 > pyridoxal 5-phosphate) have also been shown to inhibit PARP-1 activity in vitro [51]. Several unsaturated fatty acids (arachidonic acid > linoleic acid > oleic acid > palmitoleic acid > linolenic acid > γ-linolenic acid) inhibit PARP-1 activity more potently than nicotinamide in vitro [22, 51].

Endocrine Substances

Jackowski and Kun [78] have found that treatment with 3,5,3'-triiodothyronine (T_3) strongly decreased PARP-1 activity in isolated cardiomyocyte nuclei from normal and hypophysectomized male rats. In vivo treatment of male rats with T_3 (30 μg/100 g of body weight) inhibited PARP-1 activity in cardiomyocyte nuclei and significantly increased the weight of cardiac ventricles [79]. Whether PARP-1 activity is decreased or increased as a result of T_3 treatment seems to be age dependent [80]. A positive correlation between the degree of PARP-1 inhibition and cardiac ventricular enlargement in T_3-treated rats has been reported [79, 80]. Aranda et al. [81] have shown that T_3 can alter ADP-ribosylation of chromatin associated proteins in cultured rat pituitary tumor GH1 cells. T_3 inhibits also PARP-1 purified from calf thymus [82, 83]. Glucocorticoids were shown to cause a rapid loss of endogenous PAR from nonhistone high-mobility group 14 and 17 proteins in cultured mouse mammary tumor cells [84]. It has been shown that progesterone, during a period of primary estrogen stimulation, decreases PARP-1 activity in oviducts of female immature quails [85].

Taurine

Taurine, a major intracellular free β-amino acid present in leukocytes, inhibits PARP-1 in vitro by interacting with the

binding site for the adenine moiety of NAD^+ [28]. Recently, it has been demonstrated in a male rat model of stroke that taurine reduces ischemic brain damage through suppressing inflammation related to PARP-1 and nuclear factor kappa B (NF-κB) activation [86].

Antibiotics

Some antibiotics have been shown to inhibit PARP-1. Alano et al. [35] found that several tetracycline antibiotics are PARP-1 inhibitors. The rank order of potencies for investigated compounds is minocycline > doxycycline > demeclocycline > chlortetracycline [35]. Demeclocycline and chlortetracycline are natural antibiotics, while minocycline and doxycycline are semi-synthetic second-generation tetracyclines. Interestingly, minocycline is a competitive inhibitor of PARP-1, with a K_i=13.8 nM. Neuronal NAD^+ depletion and PAR formation were blocked by 100 nM minocycline [35]. Nowadays, minocycline is in clinical trials for stroke patients. The antiinflamatory effect of minocycline is also connected with PARP-1 function as a coactivator of NF-κB. However, under these conditions, PARP-1 has been shown to function in a proinflammatory manner, as demonstrated in several studies [9, 87]. The work of Kauppinen and Swanson [88] demonstrated that PARP-1 interaction with NF-κB promoted microglial metalloproteinase-9 release and neurotoxicity. Actinomycin D [44, 89], coumermycin A_1 [19], formycin B [40, 41], novobiocin [22], and showdomycin [40] have also been reported as PARP-1 inhibitors.

Metal Ions

PARP-1 inhibition/modulation is typically viewed as a favorable response; however, several investigations have found that specific metal ions, associated with adverse effects in humans, are also capable of inhibiting PARP-1 activity. These studies hint to the possible role that these ions may play in circumventing PARP-1's beneficial DNA repair activities. For example, Ito et al. [42] showed that several metals, including Cd^{2+}, Cu^{1+}, Cu^{2+}, Hg^{2+}, and Zn^{2+}, strongly inhibit PARP-1 in vitro. Zinc chloride was also shown to inhibit PARP-1 in vitro [21, 90]. Several other metal ions, Cd^{2+}, Co^{2+}, Cu^{2+}, and Ni^{2+}, inhibit H_2O_2-induced PARP-1 activity in intact cells [91]. At noncytotoxic concentrations, copper sulfate dose-dependently inhibits H_2O_2-induced poly-ADP-ribosylation in cultured HeLa S3 cells and activity of isolated recombinant PARP-1 [92]. Arsenic, as trivalent arsenite (As^{3+}) or pentavalent arsenate (As^{5+}), is naturally occurring and ubiquitously present in the environment. Interestingly, sodium arsenite decreases PARP-1 activity (IC_{50}=10 μM) in a human T-cell lymphoma-derived cell line Molt-3 [93] and, at noncytotoxic nanomolar concentrations, H_2O_2-induced poly-ADP-ribosylation in cultured HeLa S3 cells [94]. Also, some trivalent methylated arsenicals inhibit dose-dependently H_2O_2-induced poly-ADP-ribosylation in cultured human HeLa S3 cells and the activity of isolated recombinant PARP-1 [95]. It has been shown that a concentration-dependent inhibition of PARP-1 activity by sodium arsenite was probably due to disruption of PARP-1 zinc finger function [96]. Recently, several anticancer metal complexes based on platinum, ruthenium, and gold metal ions were found to inhibit PARP-1 activity in vitro (Au^{3+} > Au^{1+} > Pt^{2+} > Ru^{3+} > Ru^{2+}), with gold complexes showing the most potent effect and the lowest IC_{50} values in nanomolar range [97].

Concluding Remarks

Despite the tremendous research activities aimed at identifying inhibitors of PARP-1, the questions of what and how endogenous and naturally occurring substances regulate the activity of this enzyme in vivo remains unresolved. Bioavailability of NAD^+ naturally plays an important role in modulating PARP-1 activity. But is PARP-1 inhibition an intended biological role? Probably nicotinamide, in certain situations, directly inhibits PARP-1 activity in vivo in a classic feedback inhibition scheme. On the other hand, taking into account that nicotinamide is a moderate PARP-1 inhibitor and, in addition, a pleiotropic molecule affecting multiple systems, it is hardly imaginable that PARP-1 inhibition could rely only on this single compound. A number of endogenous molecules, mostly pleiotropic, are known to inhibit PARP-1 activity. Therefore, this suggests a complex regulation of PARP-1 activity depending on concentration, cellular location, including posttranslational modifications, protein–protein interactions, or allosteric and indirect modulation. It also suggests that the universe of naturally occurring and endogenous inhibitors of PARP-1 may be far greater than the types of compounds already identified.

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Conflict of Interest The authors declare that they have no conflict of interest.

References

1. D'Amours D, Desnoyers S, D'Silva I, Poirier GG (1999) Poly (ADP-ribosyl)ation reactions in the regulation of nuclear functions. Biochem J 342:249–268
2. Hayaishi O, Ueda K (1982) Poly- and mono(ADP-ribosyl)ation reactions. Their significance in molecular biology. In: Hayaishi O,

Ueda K (eds) ADP-ribosylation reactions. Biology and medicine. Academic Press, New York, London, pp 3–16
3. Schreiber V, Dantzer F, Amé J-C, de Murcia G (2006) Poly(ADP-ribose): novel functions for an old molecule. Nat Rev Mol Cell Biol 7:517–528
4. Kauppinen TM (2007) Multiple roles for poly(ADP-ribose)polymerase-1 in neurological disease. Neurochem Int 50:954–958
5. Skaper SD (2003) Poly(ADP-Ribose) polymerase-1 in acute neuronal death and inflammation. A strategy for neuroprotection. Ann N Y Acad Sci 993:217–228
6. Koh DW, Dawson TM, Dawson VL (2005) Poly(ADP-ribosyl)ation regulation of life and death in the nervous system. Cell Mol Life Sci 62:760–768
7. Kauppinen TM, Swanson RA (2007) The role of poly(ADP-ribose) polymerase-1 in CNS disease. Neuroscience 145:1267–1272
8. Altmeyer M, Hottiger MO (2009) Poly(ADP-ribose) polymerase 1 at the crossroad of metabolic stress and inflammation in aging. Aging (Albany NY) 1:458–469
9. Kauppinen TM, Suh SW, Berman AE, Hamby AM, Swanson RA (2009) Inhibition of poly(ADP-ribose) polymerase suppresses inflammation and promotes recovery after ischemic injury. J Cereb Blood Flow Metab 29:820–829
10. Ha HC, Snyder SH (1999) Poly(ADP-ribose) polymerase is a mediator of necrotic cell death by ATP depletion. Proc Natl Acad Sci USA 96:13978–13982
11. Ying W, Alano CC, Garnier P, Swanson RA (2005) NAD^+ as a metabolic link between DNA damage and cell death. J Neurosci Res 79:216–223
12. Andrabi SA, Dawson TM, Dawson VL (2008) Mitochondrial and nuclear cross talk in cell death: parthanatos. Ann N Y Acad Sci 1147:233–241
13. David KK, Andrabi SA, Dawson TM, Dawson VL (2009) Parthanatos, a messenger of death. Front Biosci 14:1116–1128
14. Strosznajder RP, Jesko H, Dziewulska J (2005) Effect of carvedilol on neuronal survival and poly(ADP-ribose) polymerase activity in hippocampus after transient forebrain ischemia. Acta Neurobiol Exp (Wars) 65:137–143
15. Strosznajder R, Gajkowska B (2006) Effect of 3-aminobenzamide on Bcl-2, Bax and AIF localization in hippocampal neurons altered by ischemia-reperfusion injury. The immunocytochemical study. Acta Neurobiol Exp (Wars) 66:15–22
16. Su P-H, Takehashi M, Tanaka S, Banasik M, Stedeford T, Ueda K, Muro-Cacho C, Harbison RD (2003) Hepatocellular accumulation of poly(ADP-ribose) in male ICR mice treated with a necrogenic dose of carbon tetrachloride. Res Commun Mol Pathol Pharmacol 113–114:171–179
17. Banasik M, Stedeford T, Ueda K, Muro-Cacho C, Su P-H, Tanaka S, Harbison RD (2004) Hepatoprotective effects of 6(5*H*)-phenanthridinone from chemical-induced centrilobular necrosis. Res Commun Mol Pathol Pharmacol 115–116:15–20
18. Banasik M, Stedeford T, Strosznajder RP, Takehashi M, Tanaka S, Ueda K (2011) Inhibition of poly(ADP-ribose) polymerase-1 attenuates the toxicity of carbon tetrachloride. J Enzyme Inhib Med Chem 26:883–889
19. Banasik M, Ueda K (1994) Inhibitors and activators of ADP-ribosylation reactions. Mol Cell Biochem 138:185–197
20. Purnell MR, Whish WJD (1980) Novel inhibitors of poly(ADP-ribose) synthetase. Biochem J 185:775–777
21. Rankin PW, Jacobson EL, Benjamin RC, Moss J, Jacobson MK (1989) Quantitative studies of inhibitors of ADP-ribosylation in vitro and in vivo. J Biol Chem 264:4312–4317
22. Banasik M, Komura H, Shimoyama M, Ueda K (1992) Specific inhibitors of poly(ADP-ribose) synthetase and mono(ADP-ribosyl)transferase. J Biol Chem 267:1569–1575
23. Endres M, Wang Z-Q, Namura S, Waeber C, Moskowitz MA (1997) Ischemic brain injury is mediated by the activation of poly(ADP-ribose)polymerase. J Cereb Blood Flow Metab 17:1143–1151
24. Takahashi K, Greenberg JH, Jackson P, Maclin K, Zhang J (1997) Neuroprotective effects of inhibiting poly(ADP-ribose) synthetase on focal cerebral ischemia in rats. J Cereb Blood Flow Metab 17:1137–1142
25. Strosznajder RP, Gadamski R, Czapski GA, Jesko H, Strosznajder JB (2003) Poly(ADP-ribose) polymerase during reperfusion after transient forebrain ischemia. Its role in brain edema and cell death. J Mol Neurosci 20:61–72
26. Strosznajder RP, Walski M (2004) Effects of 3-aminobenzamide on ultrastructure of hippocampal CA1 layer after global ischemia in gerbils. J Physiol Pharmacol 55:127–133
27. Drel VR, Lupachyk S, Shevalye H, Vareniuk I, Xu W, Zhang J, Delamere NA, Shahidullah M, Slusher B, Obrosova IG (2010) New therapeutic and biomarker discovery for peripheral diabetic neuropathy: PARP inhibitor, nitrotyrosine, and tumor necrosis factor-α. Endocrinology 151:2547–2555
28. Pandya KG, Patel MR, Lau-Cam CA (2010) Comparative study of the binding characteristics to and inhibitory potencies towards PARP and in vivo antidiabetogenic potencies of taurine, 3-aminobenzamide and nicotinamide. J Biomed Sci 17:S16
29. Iwashita A, Mihara K, Yamazaki S, Matsuura S, Ishida J, Yamamoto H, Hattori K, Matsuoka N, Mutoh S (2004) A new poly(ADP-ribose) polymerase inhibitor, FR261529 [2-(4-chlorophenyl)-5-quinoxalinecarboxamide], ameliorates methamphetamine-induced dopaminergic neurotoxicity in mice. J Pharmacol Exp Ther 310:1114–1124
30. Adamczyk A, Czapski GA, Jęśko H, Strosznajder RP (2005) Non-Aβ component of Alzheimer's disease amyloid and amyloid beta peptides evoked poly(ADP-ribose) polymerase-dependent release of apoptosis-inducing factor from rat brain mitochondria. J Physiol Pharmacol 56:5–13
31. Abeti R, Abramov AY, Duchen MR (2011) β-Amyloid activates PARP causing astrocytic metabolic failure and neuronal death. Brain 134:1658–1672
32. Kauppinen TM, Suh SW, Higashi Y, Berman AE, Escartin C, Won SJ, Wang C, Cho S-H, Gan L, Swanson RA (2011) Poly(ADP-ribose)polymerase-1 modulates microglial responses to amyloid β. J Neuroinflammation 8:152. doi:10.1186/1742-2094-8-152
33. Chalmers AJ (2009) The potential role and application of PARP inhibitors in cancer treatment. Br Med Bull 89:23–40
34. Javle M, Curtin NJ (2011) The potential for poly (ADP-ribose) polymerase inhibitors in cancer therapy. Ther Adv Med Oncol 3:257–267
35. Alano CC, Kauppinen TM, Valls AV, Swanson RA (2006) Minocycline inhibits poly(ADP-ribose) polymerase-1 at nanomolar concentrations. Proc Natl Acad Sci USA 103:9685–9690
36. Szabo C, Pacher P, Swanson RA (2006) Novel modulators of poly(ADP-ribose) polymerase. Trends Pharmacol Sci 27:626–630
37. Mabley JG, Wallace R, Pacher P, Murphy K, Szabó C (2007) Inhibition of poly(adenosine diphosphate-ribose) polymerase by the active form of vitamin D. Int J Mol Med 19:947–952
38. Shall S (1983) ADP-ribosylation, DNA repair, cell differentiation and cancer. In: Miwa M, Hayaishi O, Shall S, Smulson M, Sugimura T (eds) ADP-ribosylation, DNA repair and cancer. Japan Sci Soc Press, Tokyo/VNU Science Press BV, Utrecht, pp 3–25
39. Hayaishi O, Ueda K (1974) On the roles of DNA and DNA fragments in the enzymic synthesis and degradation of poly(ADP-ribose). In: Harris M (ed) Fogarty International Center Proceedings No 26: Poly(ADP-Ribose). Bethesda, MD, pp 69–76
40. Müller WEG, Zahn RK (1975) Influence of agents that act on DNA and RNA synthesis on the activity of poly(ADP-Rib) polymerase. Experientia 31:1014–1015

41. Müller WEG, Rohde HJ, Steffen R, Maidhof A, Lachmann M, Zahn RK, Umezawa H (1975) Influence of formycin B on poly-adenosine diphosphoribose synthesis in vitro and in vivo. Cancer Res 35:3673–3681
42. Ito S, Shizuta Y, Hayaishi O (1979) Purification and characterization of poly(ADP-ribose) synthetase from calf thymus. J Biol Chem 254:3647–3651
43. Benjamin RC, Cook PF, Jacobson MK (1985) Kinetic mechanism of poly(ADP-ribose) polymerase. In: Althaus FR, Hilz H, Shall S (eds) ADP-ribosylation of proteins. Springer-Verlag, Berlin, pp 93–97
44. Niedergang C, Okazaki H, Mandel P (1979) Properties of purified calf thymus poly(adenosine diphosphate ribose) polymerase. Comparison of the DNA-independent and the DNA-dependent enzyme. Eur J Biochem 102:43–57
45. Römer V, Lambrecht J, Kittler M, Hilz H (1968) Identity of nuclear NAD nucleosidase with a polyADP-ribose forming enzyme in Ehrlich ascites tumor cells. Hoppe-Seyler's Z Physiol Chem 349:109–112
46. Clark JB, Ferris GM, Pinder S (1971) Inhibition of nuclear NAD nucleosidase and poly ADP-ribose polymerase activity from rat liver by nicotinamide and 5'-methyl nicotinamide. Biochim Biophys Acta 238:82–85
47. Ueda K, Miyakawa N, Hayaishi O (1972) Poly(ADP-ribose) biosynthesis and degradation in rat liver chromatin. Hoppe-Seyler's Z Physiol Chem 353:844–845
48. Stone PR, Shall S (1973) Poly(adenosine diphosphoribose) polymerase in mammalian nuclei. Characterization of the activity in mouse fibroblasts (LS cells). Eur J Biochem 38:146–152
49. Ohgushi H, Yoshihara K, Kamiya T (1980) Bovine thymus poly(adenosine diphosphate ribose) polymerase. Physical properties and binding to DNA. J Biol Chem 255:6205–6211
50. Moonen HJJ, Geraets L, Vaarhorst A, Bast A, Wouters EFM, Hageman GJ (2005) Theophylline prevents NAD^+ depletion via PARP-1 inhibition in human pulmonary epithelial cells. Biochem Biophys Res Commun 338:1805–1810
51. Banasik M, Komura H, Ueda K (1990) Inhibition of poly(ADP-ribose) synthetase by unsaturated fatty acids, vitamins and vitamin-like substances. FEBS Lett 263:222–224
52. Tanaka Y, Matsunami N, Yoshihara K (1981) Inhibition of ADP-ribosylation of histone by diadenosine 5', 5'''-p^1, p^4-tetraphosphate. Biochem Biophys Res Commun 99:837–843
53. Suzuki H, Tanaka Y, Buonamassa DT, Farina B, Leone E (1987) Inhibition of ADP-ribosylation of histone H1 by analogs of diadenosine 5', 5'''-p^1, p^4-tetraphosphate. Mol Cell Biochem 74:17–20
54. Kun E, Kirsten E, Mendeleyev J, Ordahl CP (2004) Regulation of the enzymatic catalysis of poly(ADP-ribose) polymerase by dsDNA, polyamines, Mg^{2+}, Ca^{2+}, histones H_1 and H_3, and ATP. Biochemistry 43:210–216
55. Leone E, Suzuki H, Farina B, Pivazian AD, Karpeisky MYA (1985) Inhibition of ADP-ribosylation reaction by 2',5'-oligoadenylates. In: Althaus FR, Hilz H, Shall S (eds) ADP-ribosylation of proteins. Springer-Verlag, Berlin, pp 106–110
56. Pivazian AD, Suzuki H, Vartanian AA, Zhelkovsky AM, Farina B, Leone E, Karpeisky MYa (1984) Regulation of poly(ADP-ribose) transferase activity by 2',5'-oligoadenylates. Biochem Int 9:143–152
57. Tseng A Jr, Lee WM, Jakobovits EB, Kirsten E, Hakam A, McLick J, Buki K, Kun E (1987) Prevention of tumorigenesis of oncogene-transformed rat fibroblasts with DNA site inhibitors of poly(ADP ribose) polymerase. Proc Natl Acad Sci USA 84:1107–1111, Erratum in: Proc Natl Acad Sci USA 84:3037
58. Fujimura S, Hasegawa S, Shimizu Y, Sugimura T (1967) Polymerization of the adenosine 5'-diphosphate-ribose moiety of nicotinamide-adenine dinucleotide by nuclear enzyme. I. Enzymatic reactions. Biochim Biophys Acta 145:247–259
59. Sugimura T, Fujimura S, Hasegawa S, Shimizu Y, Okuyama H (1968) Polymerization of ADPR moiety of NAD by nuclear enzyme preparation. J Vitaminol (Kyoto) 14:135–142
60. Nishizuka Y, Ueda K, Nakazawa K, Reeder RH, Honjo T, Hayaishi O (1968) Poly adenosine diphosphate ribose synthesis and nicotinamide adenine dinucleotide transglycosidases. J Vitaminol (Kyoto) 14:143–152
61. Preiss J, Schlaeger R, Hilz H (1971) Specific inhibition of poly ADPRibose polymerase by thymidine and nicotinamide in HeLa cells. FEBS Lett 19:244–246
62. Shall S, Brightwell M, O'Farrell MK, Stone P, Whish WJD (1972) Properties of poly(ADP-ribose) polymerase in *Physarum polycephalum* and mouse fibroblasts. Hoppe-Seyler's Z Physiol Chem 353:846–847
63. Ueda K, Fukushima M, Okayama H, Hayaishi O (1975) Nicotinamide adenine dinucleotide glycohydrolase from rat liver nuclei. Isolation and characterization of a new enzyme. J Biol Chem 250:7541–7546
64. Claycomb WC (1976) Poly(adenosine diphosphate ribose) polymerase activity and nicotinamide adenine dinucleotide in differentiating cardiac muscle. Biochem J 154:387–393
65. Müller WEG, Zahn RK (1976) Poly ADP-ribosylation of DNA-dependent RNA polymerase I from quail oviduct. Dependence on progesterone stimulation. Mol Cell Biochem 12:147–159
66. Berger NA, Weber G, Kaichi AS (1978) Characterization and comparison of poly(adenosine diphosphoribose) synthesis and DNA synthesis in nucleotide-permeable cells. Biochim Biophys Acta 519:87–104
67. Levi V, Jacobson EL, Jacobson MK (1978) Inhibition of poly(ADP-ribose) polymerase by methylated xanthines and cytokinins. FEBS Lett 88:144–146
68. Terada M, Fujiki H, Marks PA, Sugimura T (1979) Induction of erythroid differentiation of murine erythroleukemia cells by nicotinamide and related compounds. Proc Natl Acad Sci USA 76:6411–6414
69. Yamamoto H, Okamoto H (1980) Protection by picolinamide, a novel inhibitor of poly (ADP-ribose) synthetase, against both streptozotocin-induced depression of proinsulin synthesis and reduction of NAD content in pancreatic islets. Biochem Biophys Res Commun 95:474–481
70. Kitamura A, Tanigawa Y, Okamoto S, Miyake Y, Shimoyama M (1981) Theophylline reduces poly(ADP-ribose) synthetase from chick embryo liver nuclei. Biochim Biophys Acta 667:63–68
71. Kristensen T, Holtlund J (1978) Poly(ADP-ribose) polymerase from Ehrlich ascites tumor cells. Properties of the purified polymerase. Eur J Biochem 88:495–501
72. Banasik M, Ueda K (1999) Dual inhibitory effects of dimethyl sulfoxide on poly(ADP-ribose) synthetase. J Enzyme Inhib 14:239–250
73. Ueda K, Banasik M (1992) Inhibition of poly(ADP-ribose) synthetase activity by tryptophan metabolites. In: Ishiguro I, Kido R, Nagatsu T, Nagamura Y, Ohta Y (eds) Advances in tryptophan research 1992. Fujita Health University Press, Toyoake , pp 141–144
74. Virág L, Szabó C (2001) Purines inhibit poly(ADP-ribose) polymerase activation and modulate oxidant-induced cell death. FASEB J 15:99–107
75. Yoshihara K, Tanaka Y (1981) ADP-ribosylation of diadenosine 5', 5'''-P^1, P^4-tetraphosphate by poly(ADP-ribose) polymerase *in vitro*. J Biol Chem 256:6756–6761
76. Suzuki H, Tornese Buonamassa D, Weisz A (1990) Inverse relationship between poly (ADP-ribose) polymerase activity and 2',5'-oligoadenylates core level in estrogen-treated immature rat. Mol Cell Biochem 99:33–39
77. Tanaka T, Yamamoto D, Sato T, Tanaka S, Usui K, Manabe M, Aoki Y, Iwashima Y, Saito Y, Mino Y, Deguchi H (2011)

Adenosine thiamine triphosphate (AThTP) inhibits poly(ADP-ribose) polymerase-1 (PARP-1) activity. J Nutr Sci Vitaminol (Tokyo) 57:192–196
78. Jackowski G, Kun E (1982) The influence of triiodothyronine on polyadenosine-diphosphoribose polymerase and RNA synthesis in cardiocyte nuclei. J Mol Cell Cardiol 14:65–70
79. Jackowski G, Kun E (1983) The effect of in vivo treatment with triiodothyronine on the in vitro synthesis of protein-poly(ADP)-ribose adducts by isolated cardiocyte nuclei and the separation of poly(ADP)-ribosylated proteins by phenol extraction and electrophoresis. J Biol Chem 258:12587–12593
80. Jackowski G, Kun E (1984) Evidence for the macromolecular basis of regulation of heart hypertrophy. Eur Heart J 5:219–224
81. Aranda A, Copp RP, Pascual A, Samuels HH (1991) Influence of thyroid hormone on ADP-ribosylation of nuclear proteins in cultured GH1 cells. FEBS Lett 279:179–183
82. Cesarone CF, Scarabelli L, Giannoni P, Orunesu M (1994) Hepatic poly(ADP-ribose) polymerase activity in rat is controlled by thyroid hormones. Biochem Biophys Res Commun 203:1548–1553
83. Giannoni P, Scarabelli L, Orunesu M, Cesarone CF (1995) In vitro effect of 3,5,3'-triiodothyronine on poly(ADP-ribosyl)ation of DNA topoisomerase I. Ital J Biochem 44:129–136
84. Tanuma S-i, Johnson LD, Johnson GS (1983) ADP-ribosylation of chromosomal proteins and mouse mammary tumor virus gene expression. Glucocorticoids rapidly decrease endogenous ADP-ribosylation of nonhistone high mobility group 14 and 17 proteins. J Biol Chem 258:15371–15375
85. Müller WEG, Totsuka A, Nusser I, Obermeier J, Rhode HJR, Zahn RK (1974) Poly(adenosine diphosphate-ribose) polymerase in quail oviduct. Changes during estrogen and progesterone induction. Nucleic Acids Res 1:1317–1327
86. Sun M, Zhao Y, Gu Y, Xu C (2011) Anti-inflammatory mechanism of taurine against ischemic stroke is related to down-regulation of PARP and NF-*k*B. Amino Acids. doi:10.1007/s00726-011-0885-3
87. Ha HC, Hester LD, Snyder SH (2002) Poly(ADP-ribose) polymerase-1 dependence of stress-induced transcription factors and associated gene expression in glia. Proc Natl Acad Sci USA 99:3270–3275
88. Kauppinen TM, Swanson RA (2005) Poly(ADP-ribose) polymerase-1 promotes microglial activation, proliferation, and matrix metalloproteinase-9-mediated neuron death. J Immunol 174:2288–2296
89. Yoshihara K (1972) Complete dependency of poly(ADP-ribose) synthesis on DNA and its inhibition by actinomycin D. Biochem Biophys Res Commun 47:119–125
90. Larsen AG, Østvold AC, Holtlund J, Kristensen T, Laland SG (1982) The inhibitory effect of Zn^{2+} on poly(ADP-ribose) polymerase activity and its reversal. Biochem J 203:511–513
91. Hartwig A, Asmuss M, Blessing H, Hoffmann S, Jahnke G, Khandelwal S, Pelzer A, Bürkle A (2002) Interference by toxic metal ions with zinc-dependent proteins involved in maintaining genomic stability. Food Chem Toxicol 40:1179–1184
92. Schwerdtle T, Hamann I, Jahnke G, Walter I, Richter C, Parsons JL, Dianov GL, Hartwig A (2007) Impact of copper on the induction and repair of oxidative DNA damage, poly(ADP-ribosyl)ation and PARP-1 activity. Mol Nutr Food Res 51:201–210
93. Yager JW, Wiencke JK (1997) Inhibition of poly(ADP-ribose) polymerase by arsenite. Mutat Res 386:345–351
94. Hartwig A, Pelzer A, Asmuss M, Bürkle A (2003) Very low concentrations of arsenite suppress poly(ADP-ribosyl)ation in mammalian cells. Int J Cancer 104:1–6
95. Walter I, Schwerdtle T, Thuy C, Parsons JL, Dianov GL, Hartwig A (2007) Impact of arsenite and its methylated metabolites on PARP-1 activity, PARP-1 gene expression and poly(ADP-ribosyl)ation in cultured human cells. DNA Repair (Amst) 6:61–70
96. Ding W, Liu W, Cooper KL, Qin X-J, de Souza Bergo PL, Hudson LG, Liu KJ (2009) Inhibition of poly(ADP-ribose) polymerase-1 by arsenite interferes with repair of oxidative DNA damage. J Biol Chem 284:6809–6817
97. Mendes F, Groessl M, Nazarov AA, Tsybin YO, Sava G, Santos I, Dyson PJ, Casini A (2011) Metal-based inhibition of poly(ADP-ribose) polymerase—the guardian angel of DNA. J Med Chem 54:2196–2206
98. Geraets L, Moonen HJJ, Wouters EFM, Bast A, Hageman GJ (2006) Caffeine metabolites are inhibitors of the nuclear enzyme poly(ADP-ribose)polymerase-1 at physiological concentrations. Biochem Pharmacol 72:902–910
99. Brightwell MD, Leech CE, O'Farrell MK, Whish WJD, Shall S (1975) Poly(adenosine diphosphate ribose) polymerase in *Physarum polycephalum*. Biochem J 147:119–129
100. Rickwood D, Osman MS (1979) Characterisation of poly(ADP-Rib) polymerase activity in nuclei from the slime mould *Dictyostelium discoideum*. Mol Cell Biochem 27:79–84
101. Benjamin RC, Gill DM (1980) Poly(ADP-ribose) synthesis in vitro programmed by damaged DNA. A comparison of DNA molecules containing different types of strand breaks. J Biol Chem 255:10502–10508
102. Banasik M, Komura H, Ueda K (1992) Specific inhibitors of poly(ADP-ribose) synthetase. In: Poirier GG, Moreau P (eds) ADP-ribosylation reactions. Springer-Verlag, New York, pp 343–350