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RESEARCH ARTICLE

D-PENICILLAMINE AS A NEONATAL NEUROPROTECTANT: CLINICAL AND NEURO DEVELOPMENTAL STUDIES

GyörgyBalla and *LajosLakatos

Department of Pediatrics, Faculty of Medicine, University of Debrecen 4012 Debrecen, NagyerdeiKrt - 98, Hungary

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ABSTRACT

Our recently published case reports (Lakatos *et al.*, 2015) – together with other healthy and highly educated patients of the long-term (28-40 years) follow-up – suggest that D-Penicillamine /DPA/-therapy of newborn infants may have significant neuroprotective effects in cases jeopardized by bilirubin-induced neurologic dysfunction (BIND) or retinopathy of prematurity (ROP).The first patient (42 ys)is now a member of a famous operahouse in Germany as an opera singer, the second one (16 ys) is excellent in music and matematics. These cases are all the more remarkable as the most common sequelae of neonatal hyperbilirubinemia /NHBI/ is the sensorineuralhearing impairment. These unexpected effects may be related to DPA capability to alter the most important gasotransmitters **(**nitric oxide /NO/ system, carbon monoxide /CO/, hydrogen sulfide /H_2S/ biosynthesis, and copper /Cu^+/ homeostasis in the brain, where Cu^+ is an endogenous modulator of neural circuit spontaneous activity**)**. According to our hypothesis DPA can modulate the function of these neurotransmitters and can protect the brain (especially the basal ganglia and retina) from injury, such as BIND and ROP.

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INTRODUCTION

The chelation therapy for non-metal overload indications continues to be investigated. Our present research article and case reports address the medical necessity of the use of a chelating agent (DPA) in the treatment of NHBI (Lakatos *et al.,* 1976; Koranyi *et al*.,1978; Yaffe and Aranda, 2010) or in the prevention of ROP (Phelps *et al.,* 2001; Christensen *et al.,* 2007; Qureshi and Kumar, 2013). Concerns remain that the most vulnerable infants are likely to acquire BIND, either because their exposure to bilirubin is not identified as severe enough to need treatment or is prolonged but slightly below current threshold levels for intervention (Bhutani and Wong, 2015). In fact, there is no specific peak total bilirubin level (TB) that is clearly associated with neurologic impairments. However, we do know of the long-lasting impact of central nervous system (CNS) changes at both functional and structural levels during brain growth (Lucey 2012; Barbara *et al.,* 2015). Recently, we published a review (Lakatos *et al.,* 2015) about DPA therapy of newborn infants. Three very impressive cases with high TB have been described to demonstrate the potential neuroprotective effects of this drug in the neonatal period.Later, in a survey, we reviewed our DPA research, which embraces a period of more than 40 years (Balla *et al.,* 2015).

Corresponding author: LajosLakatos
Department of Pediatrics, Faculty of Medicine, University of Debrecen 4012 Debrecen, NagyerdeiKrt - 98, Hungary

CASE PRESENTATION

The idea that DPA might be a suitable drug to act as a copper-binding agent for use to control NHBI occurred, serendipituously, to one of us (L.L.), while reflecting on the similarity of copper storage in Wilson's disease and neonates (Bruckmann and Zondek,1938). It is well known that all neonates have increased concentration of copper in their liver and in their brain, particularly in the basal ganglia, and a decreased concentration of a specific plasma copper-protein, ceruloplasmine, in comparison with individuals over one year old.

There were some particularly convincing cases in our practice in neonatology which deserved to be shown individually. One of them – just the first patient–was an AB0-incompatible preterm infant with 2200 gbw. After an unsuccessful exchange transfusion (ET) and a cardiac arrest necessitating resuscitation, at an extremely high serum bilirubin concentration (32.5 mg/dL = 556 micromol/L), and various

symptoms of acute bilirubin encephalopathy, intravenous administration of DPA was started. The first dose caused a spectacular fall of 6.5 mg/dL in the level in 4 hours and, under the influence of such treatment, we were able to witness a gradual disappearance of jaundice. She is now a member of a famous opera house in Germany as an opera singer. The second patient (Lakatos *et al.,* 1999), whose parents belonged to the sect of Jehovah's witness and they refused to perform ET, is now 16 years old and excellent in music and matematics. These cases are all the more remarkable as the most common sequelae of NHBI is the sensorineural hearing impairment (Worley 1996). In addition, it was our privilage to follow a number of children who are now 28-40 years of age, including sons and daughters of our relatives, colleaques, close friends. They are now highly educated persons working in health care (mostly physicians), bank, computer and building industry, *et cet.*

According to the World Health Organization report (Gilbert and Foster, 2001), ROP is emerging as a maior cause of blindness in childhood. The disease prevention seems to be especially important because the therapy of ROP cases with cryotherapy or current methods of treatment rely on highly invasive laser procedures (Trese, 2013) that themselves lead to some vision loss.

DISCUSSION

In acute neuronal insult events, such as stroke, traumatic brain or spinal cord injury, and pathological processes of secondary neuronal injury play a key role in the severity of insult and clinical prognosis (Hunt and Virmani, 2014). Along with nitric oxide (NO) and carbon monoxide (CO), hydrogen sulfide (H_2S) is regarded as the third gasotransmitter and endogenous neuromodulator and plays multiple roles in the CNS under physiological and pathological states, especially in secondary neuronal injury. The mechanisms of secondary neuronal injury exacerbating the damage caused by the initial insult includes microcirculation failure, glutamate-mediated excitotoxicity, oxidative stress, inflammatory responses, neuronal apoptosis and calcium overload. The time has come to discover the differences and similarities in the actions of the three gasotransmitters–NO, CO and H_2S (Wang, 2014).

Our observations suggest that DPA has important neuroprotective effects in cases jeopardized by BIND or ROP. These unexpected effects may be related to DPA capability to alter the nitric oxide (NO) system (Snyder 1992; Lakatos and Oroszlan, 1994; Feelisch 1998; Wigley and Sule, 2001; March *et al.,* 2013). NO synthesized in the CNS produces a myriad of effects. For example, it plays a role in the control of blood flow, learning and memory, neurotransmitter release, gene expression, immune responsiveness, and cell survival. It is also implicated in numerous pathologies such as Alzheimer's disease, Huntington's disease, and cerebral ischemia, and disorders of the basal ganglia caused by metals /Wilson's disease/, bilirubin /BIND/ or other pathologic conditions /Parkinsonism/(Ring and Serra-Mestres, 2002).

DPA is a hybrid drug in the neonatal period by its ability to modulate both oxidative stress and NO pathway. Tataranno *et al.* 2015, have summarized the new body of knowledge about antioxidant drugs for neonatal brain injury. Our recently published case reports (Lakatos *et al.,* 2015)–together with other convincing cases participated in the long-term (28-40 years) follow-up–, suggest that DPA-therapy of newborn infants may have significant neuroprotective effects in cases jeopardized by BIND or ROP – **(**despite its peripheral location, the retina or neural portion of the eye, is actually part of central nervous system/Purves 2001/). These effects based on the capability of DPA to alter the NO system, and it is a strong antioxidant (Zhu and Mao, 2012; Godínez-Rubí *et al.,* 2013; Tsukahara and Kaneko, 2014). Low molecular weight disulfides are the major products of DPA metabolism in humans (Joyce and Day, 1990). The oxidation of DPA *in vivo* may also important in the mode of action of the drug through simultaneous reduction of the reactive oxygen species (ROS). So, we can say that DPA fulfills the criteria of a hybrid drug in the neonatal period by its ability to modulate both oxidative stress and NO pathway, and can be a neuroprotective agent in the pathophysiology of neurologic dysfunction (Rahimi *et al.,* 2014). Moreover, DPA irreversibly binds to primary aldehydes and scavangesperoxinitrite. In isolated rat brain mitochondria, DPA reduced peroxinitrite-induced mitochondrial respiratory failure, accompanied by a decrese in 4-Hydroxynonenal (4-HNE) level. In addition, administration this drug in the acute phase of mouse traumatic brain injury (TBI) model aided recovery. The carbonyl scavenger DPA binds primarily to aldehydes in an irreversible manner which inhibits their damaging effects and has also been shown to scavenge peroxynitrite as well. Acute DPA administration has previously been shown to improve neurological recovery in the mouse concussive head injury model and to protect brain mitochondria (Bains and Hall, 2012; Arent *et al.,* 2014).Furthermore, DPA attenuates oxygen radical induces pulmonary hypertension in the newborn pigs (Oroszlán *et al.,* 1990) and probably prevents bronchopulmonary dysplasia (BPD) in premature babies.

Other endogenously generated small-molecule species, such as CO and H_2S, have also been shown to possess important signaling properties. These species play critical roles in numerous biological processes, including regulation of enzyme activity, protein structure and function, and cellular defense.

DPA and CO production

The gaseous neurotransmitter, NO, has already been shown to have an important regulatory function. However, little is known about the role of other gasotransmitters. Previous studies indicate that CO has a dual behavioral role within the anterior hypothalamus, exerting control over both reproductive and anxiety behaviors, and that its similarities and contrasts to NO may stem from the variable regulation of the two CO-producing enzymes: heme oxigenase-1 and -2 /HO-1 and HO-2/ (Robison 2014). HO-1 is an inducible 32-kDa protein, while HO-2 is a constitutively synthesized 36-kDa protein and generally is unresponsive to any of the inducers of HO-1 (Morimatsu *et al.,* 2012). The heme is an essential prosthetic group of enzymes with functions such as oxygen storage and transport (hemoglobin and myoglobin), electron transport and energy generation (NADPHoxidase, guanylylcyclase and cytochrome P450 family); and enzymatic systems such as catalase, peroxidase, nitric oxide synthase (NOS), and cyclooxygenase.

Table 1. Possible effects of D-Penicillamine (DPA) in the neonatal period (a schematic presentation)

Defends against	Prevents	Alters
• Reactive oxygen species	• Secondary neuronal injury	• Oxidative stress
• Peroxinitrite	• Neurologic dysfunction	• NO pathway
• Reactive carbonyl species	• BIND or ROP	• Lipid peroxidation
• Aldehydes	• Decrese in 4-Hydroxynonenal level	• CO-producing (HO-1 and HO-2) and
• Lead burden	•Traumatic brain injury	• Endogen antioxidant enzymes (as a part of age related effects)
• Excess of copper and iron	•Hydrogen peroxide-induced cytotoxicity	• Hydrogen sulfide (H_2S) biosynthesis
• Excess of vascular endothelial growth factor	•Oxygen radical induces pulmonary hypertension	• Neuronal Ca^{++} concentration
• Excess of hydrogen sulfide	•Bronchopulmonary dysplasia	• Dynamic regulation of copper signaling
• Lipidperoxidation of the biomembranes	•Damage of thebrain mitochondria	• Arachidonic acid metabolism
• Bilirubin production		• Synthesis of inducible nitric oxide synthase
• Copper mismanagement		•VEGF-mediated vascular morphogenesis
		•The vascular tone regulations of the cerebral blood vessels

HO-1 induction leads to increased heme breakdown (e.g., hemolytic diseases and NHBI),resulting in the production of iron, CO, and biliverdin IX, which is subsequently reduced to bilirubin IX by biliverdinreductase. There is also evidence that HO-2 participates in a multitude of housekeeping functions, mainly in the brain, since it is the most prominent expressed isoform and the first to respond against oxidative stress. Indeed, the relevance of HO-2 for the CNS is emphasized by evidence showing that the continuous and regulated endogenous CO production by the activity of this enzyme is a key factor formaintaining the physiological function in neuronal cells and the vascular tone regulations of the cerebral blood vessels (Muñoz-Sánchez and Chánez-Cárdenas, 2014). It is also an interesting phenomenon that DPA inhibits the rate limited enzyme (HO-1) in heme metabolism only in neonates (Oroszlán*et al.,*1983/a) and – most likely – it has no or little effect on HO-2. As a part of *age related effects* (Lakatos*et al.*, 1982), this drug induces cytochrome P-450 in the neonatal period (Oroszlán*et al.,* 1983/b). The selective inhibition of HO-1 isoform is generally preferable (Pittalà*et al.,*2013). Because those enzymes that play an important role in antioxidant defense and drug metabolism are heme proteins, it can be assumed that in preventing hyperbilirubinemia, ROP and oxygen toxicity, the mechanism of action of DPA is identical: the protection of biomembranes against lipid peroxidation caused by free radical.

DPA exerts inhibitory action on hydrogen sulfide biosynthesis (Brancaleone et al., 2015)

Hydrogen sulfide (H_2S) is regarded as the third gasotransmitter and endogenous neuromodulator and plays multiple roles in CNS under physiological and pathological states, especially in secondary neuronal injury (Szabó 2007; Bianco and Fukuto, 2015). At high H_2S content of CNS elevates neuronal Ca^{++} concentration and may contribute to the formation of calcium overload in secondary neuronal injury. Above mentioned inhibitory effect of H_2Scan be also beneficial to develop of BIND or ROP.

Copper is an endogenous modulator of neural circuit spontaneous activity

Dodani *et al.,* 2014 have shown that acute copper chelation in a dose-dependentmanner in dissociated hippocampal culture and intact developing retina increased the cell participation and frequencyof calcium transients during spontaneous activity.

Consequently, the above mentioned inhibitory effect of H_2S can be also beneficial to develop of BIND or ROP.

Copper is an endogenous modulator of neural circuit spontaneous activity

Dodani *et al.,* 2014 have shown that acute copper chelation in a dose-dependent manner in dissociated hippocampal culture and intact developing retina increased the cell participation and frequency of calcium transients during spontaneous activity.

Moreover,modulation of cellular copper levels through genetic knockdownof the copper ion channel copper transporter 1 /CTR1/ led to a similar increase in synchronization of calcium transients, indicating that this proteinis involved in dynamic regulation of copper signaling, which in turn affects neural activity.In addition, these data implicate Cu^{+}signaling in neuronal signaling, suggesting that alterations in brain copper homeostasis in genetic disorders like Wilson's disease, as well as more complex neurodegenerative diseases such as Alzheimer's and Huntington's diseases and prion encephalopathies that are linked to copper mismanagement, can contribute to misregulation of cell−cell communication.

DPA is actually the drug most extensively used to treat copper overload in Wilson's disease and as such is a very attractive building block for the design of chelating agents which is useful in neonates who have increased concentration of copper in their brain, particularly in the basal ganglia (Jullien*et al.,* 2014).

Conclusion

Our observations – together with other convincing cases participating in the long-term (28-40 years) follow-up – suggest that DPA-therapy in the neonatal period may have significant neuroprotective effects in cases jeopardized by BIND or ROP. According to our hypothesis DPA can modulate the function of gasotransmitters and alters the copper homeostasis in the brain, so, it can protect the brain (especially the basal ganglia and retina) from various injury, such as BIND and ROP. In **Table 1**, we summarize the various effects of DPA in the neonatal period. During the last 40 years Hungarian neonatologists have treated a number of term and preterm infants with DPA to treat severe jaundice and prevent retinopathy. *No acute or long-term adverse effects or any late*

complications of this treatment protocol have been observed during several years of follow-up. According to our opinion, the most important discovery" of DPA-project is that this drug should be undoubtedly *effective*(jaundice, lead burden(Lakatos 1993), and may be in the prevention of ROP(a well-designed large multicenter randomized controlled trial is required)and vertical infection of HIV (Lakatos2013), *safe*(more than 25-30 000 cases only in Hungary without any side effects!)andquite *inexpensive*(even more for the developing countries!), and it can be used in *unusual high doses* (Oroszlán *et al.,*1987) in the neonatal period.

LIST OF ABBREVATIONS

BIND - Bilirubin-induced neurologic dysfunction
CO - Carbon monoxide
CNS -Central Nervous System
CTR1 -Copper transporter 1
Cu^+ - Copperion
DPA - D-Penicillamine
ET - Exchange transfusion
H_2S - Hydrogen sulfide
4-HNE - 4-Hydroxynonenal level
NHBI - Neonatal hyperbilirubinemia
NO - Nitric oxide
RCS - Reactive carbonyl species
ROP - Retinopathy of prematurity
ROS - Reactive oxygen species
TB - Total bilirubin level
TBI - Traumatic brain injury
VEGF - Vascular endothelial growth factor

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Authors' contributions

Both authors contributed equally to this work. The authors discussed the results and implications and commented on the manuscript at all stages.

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