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# Copper Concept of Bilirubin-Binding Neurologic Dysfunction (BIND): Role of NO, CO and $H_2S$ in the Neonatal CNS

**Lajos Lakatos[1]*, György Balla[2] and István Pataki[1]**

[1]*Faculty of Medicine, Department of Pediatrics, University of Debrecen, Debrecen, Hungary*

[2]*Member of the Hungarian Academy of Science, Faculty of Medicine, Department of Pediatrics, University of Debrecen, Debrecen, Hungary*

***Corresponding Author**: Lajos Lakatos, Faculty of Medicine, Department of Pediatrics, University of Debrecen, Debrecen, Hungary.

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## Abstract

A large number of studies have long been made on the possible biochemical transformations of unconjugated bilirubin (UCB) which is formed during the decomposition of hemoglobin. Its photochemical and redox reactions have been paid particular attention but relevant publications are not including the molecular biochemistry of UCB and metal interactions. The literature review and our more than 4 decades experiences have helped us to perform a new concept of the development of bilirubin-induced neurologic dysfunction (BIND). UCB has a strong affinity for the basal ganglia (BG) because the latter are also target brain regions for divalent metal (Cu, Fe, Zn etc.). The immaturity and increased vulnerability of neurons in the neonatal period play also an important role in the pathogenesis of BIND. On the basis of abundant research data and hypotheses, according to our concept, the BIND is a neurodegenerative and neurodevelopmental disease of immature brain caused by free metals and UCB-Cu complex (as pro-oxidant) accumulating in the BG and other parts of central nervous system (CNS) relevant to BIND. During this process we have to account with gasotransmitters. Along with nitric oxide (NO) and carbon monoxide (CO), hydrogen sulfide (H2S) is also a potent endogenous neuromodulator and plays multiple roles in the CNS both in physiological and pathological conditions, especially in secondary neuronal injury.

***Keywords:*** *Autism Spectrum Disorders (ASD); Bilirubin-Induced Neurologic Dysfunction; Reactive Oxygen Species; Copper Dyshomeostasis; Neurodegeneration; D-Penicillamine in the Neonatal Period; Gasotransmitters*

## Abbrevation

ASD: Autism Spectrum Disorders; BG: Basal Ganglia; BIND: Bilirubin-Induced Neurologic Dysfunction; CO: Carbon Monoxide; CNS: Central Nervous System; D-PA: D-Penicillamine; HO: Heme Oxigenase; H2S: Hydrogen Sulfide; NO: Nitric Oxide; iNOS: Inducible Nitric Oxide Synthase; NHBI: Neonatal Hyperbilirubinemia; ROP: Retinopathy of Prematurity; ROS: Reactive Oxygen Species; UCB: Unconjugated Bilirubin

## Introduction

Our recently published case report [1] and other healthy and highly educated patients of the long-term (23-42 years) follow-up suggest that D-PA therapy of newborn infants may have a potent neuroprotection in cases jeopardized by BIND or retinopathy of prematurity (ROP). The first patient (43 ys) is now a member of a famous operahouse as an opera singer, and a number of children can be found in excellent positions among sons and daughters of our relatives, colleagues, close friends: physicians, musicians, matematicians, bank and computer businesspersons, professional diplomat (with knowledge of 4 languages) and architects etc. The most vulnerable infants are likely to acquire BIND, either because their exposure to bilirubin is not consider severe enough to need treatment or they discharge too early from the hospital. We do know of the long-lasting impact of CNS changes at both functional and structural levels during brain growth [2], and in acute neuronal insults playing a key role in the severity of insult and clinical prognosis [3].

## Method

This research article has needed to review the literature data accessible by the authors in their Institute and on the Web.

## Results

The results of D-PA therapy in the neonatal period (treatment of various form of NHBI, prevention of ROP and the mechanisms of this drug in these conditons) are reviewing in a book published in 2016 [4].

## Discussion

Along with NO and CO, hydrogen sulfide ($H_2S$) is regarded as the third gasotransmitter. These endogenous neuromodulators play multiple roles in the CNS under physiological and pathological states, especially in secondary neuronal injury. The latter exacerbating the damage caused by the initial insult includes microcirculation failure, glutamate-mediated excitotoxicity, oxidative stress, inflammatory responses, neuronal apoptosis and calcium overload. There are a number of differences and similarities in the actions of these gasotransmitters [5,6]. NO synthesized in the CNS produces a myriad of effects: controling blood flow, learning and memory, neurotransmitter release, gene expression, immune responsiveness, and cell survival. It is also implicated in numerous pathologies such as Alzheimer disease, Huntington's disease, and cerebral ischemia, and disorders of the basal ganglia (BG) caused by metals (in Wilson's disease), Cu-bilirubin complex (in BIND) or other pathologic conditions (in Parkinsonism) [7]. D-PA modulates both oxidative stress and NO pathway in the neonatal period [8]. Tataranno., *et al.* [9] have summarized the new body of knowledge about antioxidant drugs for neonatal brain injury. D-PA-therapy of newborn infants may also have significant neuroprotective effects in cases jeopardized by BIND or ROP – (the retina is actually part of CNS [10]). These effects based on the capability of D-PA to alter the NO system, and it is a strong antioxidant [11]. Low molecular weight disulfides are the major products of D-PA metabolism in humans [12], and they 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 D-PA fulfills the criteria of a hybrid drug in the neonatal period, and can be a neuroprotective agent in the pathophysiology of neurologic dysfunction [13]. This drug irreversibly binds to primary aldehydes and scavenges peroxinitrite. In isolated rat brain mitochondria, D-PA reduced peroxinitrite-induced mitochondrial respiratory failure, accompanied by a decrease in 4-Hydroxynonenal (4-HNE) level [14,15]. Acute D-PA administration has improved neurological recovery in the mouse concussive head injury model and protected brain mitochondria [16]. Furthermore, D-PA attenuates oxygen radical induces pulmonary hypertension in the newborn pigs [17], and probably prevents bronchopulmonary dysplasia in premature babies. Other endogenously generated gasotransmitters, such as CO and H2S, have also been shown to possess important signaling properties. These species play important roles in numerous biological processes: regulation of enzyme activity, protein structure and function, and cellular defense. Previous studies indicate that CO has a dual behavioral role within the anterior hypothalamus controling both reproductive and anxiety behaviors, and together with NO may regulate the two CO producing enzymes: heme oxigenase-1 and -2 (HO-1 and HO-2) [18]. HO-1 is an inducible 32-kDa protein, while HO-2 is a constitutively synthesized 36kDa protein and generally is unresponsive to any of the inducers of HO-1 [19]. 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 (NADPH oxidase, guanylylcyclase and cytochrome P-450 family). It is a very important part of the enzymatic systems such as catalase, peroxidase, iNOS, and cyclooxygenase. There is also evidence that HO-2 participates in a multitude of housekeeping functions in the brain, since it is the first to respond against oxidative stress. Indeed, the important role 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 essential for maintaining the physiological function in neuronal cells and the vascular tone regulations of the cerebral blood vessels [20]. It is also an interesting phenomenon that D-PA inhibits the rate limited enzyme (HO-1) in heme metabolism only in neonates [21] and, most likely, it does not have any effects on HO-2. As a part of its age related effects D-PA induces cytochrome P-450 only in the neonatal period. The selective inhibition of HO-1 isoform is generally preferable [22]. 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 mechanisms of action of DPA is the same: protection against lipid peroxidation caused by free radical. D-PA exerts inhibitory action on $H_2S$ biosynthesis [23]. This gaseous neurotransmitter is regarded as endogenous neuromodulator and plays multiple roles in CNS under physiological and pathological states, especially in secondary neuronal injury [24]. At high $H_2S$ content of CNS elevates neuronal $Ca^{++}$ concentration and may contribute to the formation of calcium overload in secondary neuronal injury. Dodani., *et al.* [25] have shown that acute copper chelation in 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 knock down of the copper ion channel copper transporter 1 (CTR1) led to a similar increase in synchronization of calcium transients, 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 other, more complex neurodegenerative diseases (ie. Alzheimer' or Huntington's diseases and prion encephalopathies) that are linked to copper mismanagement and can contribute to misregulation of cell–cell communication. D-PA is actually the drug most extensively used to treat copper overload in Wilson's disease and it is useful in neonates who have a high copper content in the brain, particularly in the BG [26].

## Conclusion

Our observations – together with other convincing cases participating in the long-term (23-40 years) follow-up – suggest that D-PA-therapy in the neonatal period may have significant neuroprotective effects in cases jeopardized by BIND or ROP. According to our concept, D-PA can alter the function of NO, CO and $H_2S$ and the copper homeostasis in the brain; so, it can protect the brain (especially the BG and retina) from various injury, such as BIND and ROP. During the last 40 years neonatologists working in Hungary and in the rest of the world treated a number of term and preterm infants with D-PA without any serious adverse effects. According to our opinion, the most important "discovery" of D-PA-project is that this drug should be undoubtedly effective (jaundice, lead burden [27], and may be in the prevention of ROP [28] - a well-designed large multicenter randomized controlled trial is required - safe, - more than 25-30000 cases only in Hungary without any side effects, and quite inexpensive - even more for the developing countries!), and it can be used in unusually high doses as a short-term therapy in the neonatal brain's defence [29-31].

## Addendum

The following comment has not convincing scientific evidence. It is rather an interesting observation: during long-term follow up studies (3-36 years - n = 550) we found only 1 ASD in the children and adults who were treated with D-PA in their neonatal period ("New Prevalence Numbers for 2014: 1 in 45 US Children have autism" [32]). This 30 years old male patient was born as a premature infant and had a serious hyperbilirubinemia. He was treated with D-PA without success, because exchange transfusion was necessary to perform [33].

## Declarations

The authors had the approval by the institution's board (Regional and Institutional Research Ethics Committee of the Medical and Health Science Center of the University of Debrecen) to treat newborns with D-PA and conduct long-term follow up studies.

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## Authors' Contributions

LL, GB, and IP are eaqually contributed. All authors read and approved the final manuscript.

## Authors' Information

None.

## Competing Interests

The authors declare that they have no competing interests.

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